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(21) International Application Number: PCT/CA99/00926 (22) International Filing Date: 5 October 1999 (05.10.99) (30) Priority Data: 60/103,564 7 October 1998 (07.10.98) US (71) Applicant (for all designated States except US): MERCK FROSST CANADA & CO. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): BELLEY, Michel [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). LACHANCE, Nicholas [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). LABELLE, Marc [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). GALLANT, Michel [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). CHAURET, Nathalie [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). LI, Chun [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). TRIMBLE, Laird,	A. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). (74) Agents: COTE, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: PROSTAGLANDIN RECEPTOR LIGANDS		
(57) Abstract <p>Compounds and methods for treating prostaglandin mediated diseases, and certain pharmaceutical compositions thereof are disclosed. The compounds are represented by formula (II): Ar¹-W-Ar²-X-Q. The compounds of the invention are structurally different from NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.</p>		

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5 TITLE OF THE INVENTION
PROSTAGLANDIN RECEPTOR LIGANDS

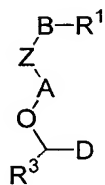
BACKGROUND OF THE INVENTION

10 This invention relates to compounds and methods for treating prostaglandin mediated diseases, and certain pharmaceutical compositions thereof. More particularly, the compounds of the invention are structurally different from NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.

15 Two review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids: From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Macclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87. An article from *The*
20 *British Journal of Pharmacology* (1994, 112, 735-740) suggests that Prostaglandin E₂ (PGE₂) exerts allodynia through the EP₁ receptor subtype and hyperalgesia through EP₂ and EP₃ receptors in the mouse spinal cord.

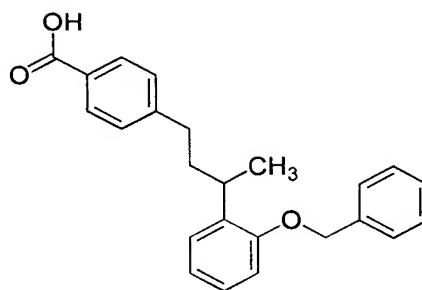
Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered,
25 have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase
30 inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

PCT application nos WO 96/06822 (March 7, 1996), WO
35 96/11902 (April 25, 1996), WO 97/00863 (January 9, 1997), WO 97/00864 (January 9, 1997), WO 96/03380 (February 8, 1996), and EP 752421-A1 (January 08, 1997) disclose compounds represented by Formula I as being useful in the treatment of prostaglandin mediated diseases.



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I



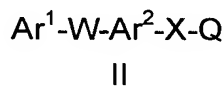
Ia

wherein:

- 10 A is phenyl, naphthyl, 5- or 6- membered heteroaryl
 B is phenyl, 5- or 6- membered heteroaryl or a further defined keto-dihydro
 ring;
 D is phenyl, 5- or 6- membered heteroaryl;
 R¹ is COOH, carboxyalkyl, tetrazolyl(alkyl);
 15 R³ is H or alkyl, and
 Z is an alkylene bridge containing 0-1 nitrogen atom or a further defined
 unsaturated bridge.
 Compound Ia is one of the compounds specifically claimed.

20 SUMMARY OF THE INVENTION

The present invention relates to compounds represented by
 formula II:



- 25 as well as pharmaceutically acceptable salts and hydrates thereof, wherein:
 Ar¹ is an aryl or heteroaryl group, optionally substituted with R¹
 or R³;

R¹ is Y_m-R², Y_m-Ar³, halogen, N(R⁵)₂, CN, NO₂, C(R⁶)₃,
 CON(R⁵)₂, S(O)_nR⁷ or OH;

- 30 Y represents a linker between R² or Ar³ and Ar¹ containing 0-4
 carbon atoms and not more than one heteroatom selected from O, N and S,
 said linker optionally containing CO, S(O)_n, -C=C- or an acetylenic group, and
 said linker being optionally substituted by R²;

m is 0 or 1;

- 35 n is 0, 1 or 2;

5 R^2 represents H, F, CHF_2 , CF_3 , lower alkyl or hydroxyC₁₋₆ alkyl, or two R^2 groups may be joined together and represent a carbocyclic ring of up to six members, said ring containing not more than one heteroatom selected from O, N and S;

10 Ar^3 represents an aryl or heteroaryl group, optionally substituted with R^3 ;

R^3 is R^4 , halogen, haloC₁₋₆alkyl, $\text{N}(\text{R}^5)_2$, CN, NO_2 , $\text{C}(\text{R}^6)_3$, $\text{CON}(\text{R}^5)_2$, OR^4 , SR^4 or $\text{S}(\text{O})_n\text{R}^7$;

R^4 is H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;

15 R^5 is R^4 , Ph or Bn, or two R^5 groups in combination with the atom to which they are attached represent a ring of up to 6 members containing carbon atoms and up to 2 heteroatoms selected from O, N and S;

R^6 is H, F, CF_3 or lower alkyl, or two R^6 groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;

20 R^7 is lower alkyl, lower alkenyl, lower alkynyl, CHF_2 , CF_3 , $\text{N}(\text{R}^5)_2$, $\text{Ph}(\text{R}^8)_2$ or $\text{CH}_2\text{Ph}(\text{R}^8)_2$;

R^8 is R^4 , OR^4 , SR^4 or halogen

25 W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $\text{S}(\text{O})_n$, C=C or an acetylenic group, and optionally being substituted with R^9 ;

R^9 is R^2 , lower alkenyl, lower alkynyl, OR^4 or SR^4 ;

Ar^2 represents an aryl or heteroaryl group, optionally substituted with R^3 ;

30 R^{10} represents R^4 , halogen, $\text{N}(\text{R}^5)_2$, CN, NO_2 , $\text{C}(\text{R}^6)_3$, OR^4 , SR^4 or $\text{S}(\text{O})_n\text{R}^7$;

35 X represents a linker which is attached to Ar^2 ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, $\text{S}(\text{O})_n$, C=C or an acetylenic group, and said linker being optionally substituted with R^{11} ;

R^{11} is R^9 ;

5 Q represents a member selected from the group consisting of:
CO₂H, tetrazole, SO₃H, hydroxamic acid, CONHSO₂R¹² and SO₂NHCOR¹²;

R¹² represents a member selected from the group consisting of:
CF₃, lower alkyl, lower alkenyl, lower alkynyl and ZAr⁴, wherein Z is an
optional linker containing 0-4 carbon atoms, optionally substituted with R¹³;

10 R¹³ is R⁹;

Ar⁴ is an aryl or heteroaryl group optionally substituted with R¹⁴,
and

R¹⁴ is R¹⁰ or NHCOMe.

15 Pharmaceutical compositions and methods of treatment are
also included.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds represented by
formula II:



as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar¹ is an aryl or heteroaryl group, optionally substituted with R¹
or R³;

25 R¹ is Y_m-R², Y_m-Ar³, halogen, N(R⁵)₂, CN, NO₂, C(R⁶)₃,
CON(R⁵)₂, S(O)_nR⁷ or OH;

Y represents a linker between R² or Ar³ and Ar¹ containing 0-4
carbon atoms and not more than one heteroatom selected from O, N and S,
said linker optionally containing CO, S(O)_n, -C=C- or an acetylenic group, and
30 said linker being optionally substituted by R²;

m is 0 or 1;

n is 0, 1 or 2;

R² represents H, F, CHF₂, CF₃, lower alkyl or hydroxyC₁₋₆ alkyl,
or two R² groups may be joined together and represent a carbocyclic ring of
35 up to six members, said ring containing not more than one heteroatom
selected from O, N and S;

Ar³ represents an aryl or heteroaryl group, optionally substituted
with R³;

- 5 R^3 is R^4 , halogen, haloC₁₋₆alkyl, $N(R^5)_2$, CN, NO_2 , $C(R^6)_3$, $CON(R^5)_2$, OR^4 , SR^4 or $S(O)_nR^7$;
 R^4 is H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;
 R^5 is R^4 , Ph or Bn, or two R^5 groups in combination with the atom to which they are attached represent a ring of up to 6 members
10 containing carbon atoms and up to 2 heteroatoms selected from O, N and S;
 R^6 is H, F, CF_3 or lower alkyl, or two R^6 groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;
 R^7 is lower alkyl, lower alkenyl, lower alkynyl, CHF_2 , CF_3 ,
15 $N(R^5)_2$, $Ph(R^8)_2$ or $CH_2Ph(R^8)_2$;
 R^8 is R^4 , OR^4 , SR^4 or halogen
W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and optionally being
20 substituted with R^9 ;
 R^9 is R^2 , lower alkenyl, lower alkynyl, OR^4 or SR^4 ;
 Ar^2 represents an aryl or heteroaryl group, optionally substituted with R^3 ;
 R^{10} represents R^4 , halogen, $N(R^5)_2$, CN, NO_2 , $C(R^6)_3$, OR^4 , SR^4
25 or $S(O)_nR^7$;
X represents a linker which is attached to Ar^2 ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and said linker being
30 optionally substituted with R^{11} ;
 R^{11} is R^9 ;
Q represents a member selected from the group consisting of: CO_2H , tetrazole, SO_3H , hydroxamic acid, $CONHSO_2R^{12}$ and SO_2NHCOR^{12} ;
 R^{12} represents a member selected from the group consisting of:
35 CF_3 , lower alkyl, lower alkenyl, lower alkynyl and ZAr^4 , wherein Z is an optional linker containing 0-4 carbon atoms, optionally substituted with R^{13} ;
 R^{13} is R^9 ;

5 Ar⁴ is an aryl or heteroaryl group optionally substituted with R¹⁴,
and
R¹⁴ is R¹⁰ or NHCOMe.

10 As used herein, the following terms and definitions apply unless
indicated otherwise.

The following abbreviations have the indicated meanings:

	Ac	=	acetyl
	AIBN	=	2,2'-azobisisobutyronitrile
	Bn	=	benzyl
15	DHP	=	2,3-dihydro-4H-pyran
	DIBAL	=	diisobutyl aluminum hydride
	DIPHOS	=	1,2-bis(diphenylphosphino)ethane
	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	N,N-dimethylformamide
20	DMSO	=	dimethyl sulfoxide
	EDCI	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	Et ₃ N	=	triethylamine
	Fur	=	furandiyl
25	HBBS	=	Hanks balanced salt solution
	HEPES	=	N-[2-hydroxyethyl]piperazine-N'-[2- ethanesulfonic acid]
	KHMDS	=	potassium hexamethyldisilazane
	LDA	=	lithium diisopropylamide
30	LPS	=	lipopolysaccharide
	MCPBA	=	metachloroperbenzoic acid
	MES	=	2-[N-morpholino]ethanesulfonic acid
	Ms	=	methanesulfonyl = mesyl
	MsO	=	methanesulfonate = mesylate
35	NBS	=	N-bromosuccinimide
	NCS	=	N-chlorosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate

5	PDC	=	pyridinium dichromate
	Ph	=	phenyl
	Phe	=	benzenediyl
	PPTS	=	pyridinium p-toluenesulfonate
	pTSA	=	p-toluenesulfonic acid
10	Pye	=	pyridinediyl
	r.t.	=	room temperature
	rac.	=	racemic
	Tf	=	trifluoromethanesulfonyl = triflyl
	TfO	=	trifluoromethanesulfonate = triflate
15	Th	=	2- or 3-thienyl
	THF	=	tetrahydrofuran
	Thi	=	thiophenediyl
	THP	=	tetrahydropyran-2-yl
	Thz	=	thiazol-2-yl
20	TLC	=	thin layer chromatography
	Ts	=	p-toluenesulfonyl = tosyl
	TsO	=	p-toluenesulfonate = tosylate
	Tz	=	1H (or 2H)-tetrazol-5-yl
	C ₃ H ₅	=	allyl
25	Alkyl group abbreviations		
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
30	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
35	c-Bu	=	cyclobutyl
	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

The terms alkyl, alkenyl, and alkynyl mean linear, branched, and cyclic structures and combinations thereof.

- 5 "Alkyl" and the alkyl portions of alkoxy, arylalkyl, alkylaryl and the like include "cycloalkyl" and "lower alkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, and the like.
- 10 "Lower alkyl" includes "lower cycloalkyl" and means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, and the like.
- "Cycloalkyl" includes "lower cycloalkyl" and means a hydrocarbon, containing one or more rings of from 3 to 12 carbon atoms, with
- 15 the hydrocarbon having up to a total of 20 carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1-bicyclo[4.4.0]decyl, and the like.
- "Lower cycloalkyl" means a hydrocarbon containing one or more rings of from 3 to 7 carbon atoms, with the hydrocarbon having up to a total of
- 20 7 carbon atoms. Examples of lower cycloalkyl groups are cyclopropyl, cyclopropylmethyl, cyclobutyl, 2-cyclopentylethyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, and the like.
- The term "alkenyl" includes "cycloalkenyl" and "lower alkenyl" and means alkenyl groups of 2 to 20 carbon atoms. Examples of alkenyl
- 25 groups include allyl, 5-decen-1-yl, 2-dodecen-1-yl, and the like.
- "Lower alkenyl" includes "lower cycloalkenyl" and means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.
- 30 "Cycloalkenyl" includes "lower cycloalkenyl" and means alkenyl groups of 3 to 20 carbon atoms, which include a ring of 3 to 12 carbon atoms, and in which the alkenyl double bond may be located anywhere in the structure. Examples of cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-vinyladamant-1-yl, 5-methylene-dodec-1-yl and the like.
- 35 "Lower cycloalkenyl" means alkenyl groups of 3 to 7 carbon atoms, which include a ring of 3 to 7 carbon atoms and in which the double bond may be located anywhere in the structure. Examples of lower cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-cyclopentylethen-1-yl, and the like.

5 The term "alkynyl" includes "cycloalkynyl" and "lower alkynyl" and means alkynyl groups of 2 to 20 carbon atoms. Examples of alkynyl groups are ethynyl, 2-pentadecyn-1-yl, 1-eicosyn-1-yl, and the like.

 "Lower alkynyl" includes "lower cycloalkynyl" and means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include
10 ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

 "Cycloalkynyl" includes "lower cycloalkynyl" and means alkynyl groups of 5 to 20 carbon atoms, which include a ring of 3 to 20 carbon atoms. The alkynyl triple bond may be located anywhere in the group, with the proviso that if it is within a ring, such a ring must be of 10 members or greater.
15 Examples of cycloalkynyl are cyclododecyn-3-yl, 3-cyclohexyl-1-propyn-1-yl, and the like.

 "Lower cycloalkynyl" means alkynyl groups of 5 to 7 carbon atoms which include a ring of 3 to 5 carbon atoms. Examples of lower cycloalkynyl are cyclopropylethynyl, 3-(cyclobutyl)-1-propynyl, and the like.

20 Halogen includes F, Cl, Br and I. When a group is "halogenated", it is substituted with one or more halogen atoms, up to the maximum number of positions available for substitution, i.e., it is "perhalogenated".

 The definition of any substituent (e.g., R^6 , R^{10} , etc.) in a
25 particular molecule is independent of its definition elsewhere in the molecule. Thus, $-N(R^5)_2$ represents $-NHH$, $-NHCH_3$, $-NHC_6H_5$, and the like.

 Examples of rings formed when two R^2 groups join include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, oxetane, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene,
30 tetrahydrothiopyran, pyrrolidine and piperidine.

 The heterocycles formed when two R^5 groups join through N include pyrrolidine, piperidine, morpholine, thiamorpholine, piperazine and N-methylpiperazine.

35 Aryl and the aryl portions of arylalkyl, aryloxy, arylalkoxy and the like refer to aromatic as well as partially aromatic 6-12 membered ring systems. Examples include benzene, naphthalene, biphenyl and tetrahydronaphthalene.

 Heteroaryl and the heteroaryl portion of heteroarylalkyl, heteroarylalkoxy, heteroaryloxy and the like refer to 5-15 membered aromatic

5 and partially aromatic ring systems, containing 1-4 heteroatoms selected from O, S and N. Examples include pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, benzothiazole, 1,3,4-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, pyrrole and methylenedioxyphenyl.

10 Haloaryl and haloheteroaryl refer to aryl and heteroaryl groups respectively having at least one halo atom attached, up to perhalogenated, as indicated above. Haloalkyl refers to alkyl groups which have one or more halogen atoms attached, including up to the maximum number of positions which can be substituted, i.e., perhalogenated alkyl groups. In
15 haloalkylarylalkoxy, the terminal alkyl portion is halogenated. In haloarylalkoxy, the aryl portion is halogenated, and in haloheteroarylalkoxy the heteroaryl portion is halogenated.

Aryl, heteroaryl and other groups are termed optionally substituted as described herein. When a moiety is optionally substituted, this
20 means that the moiety is unsubstituted or is substituted with 1-5 of the substituent groups, as permitted with respect to the availability for substitution. In particular, this applies to Ar¹, which is optionally substituted with 1-5 R¹ and/or R³ groups. Y is optionally substituted with 1-5 R² groups. Ar³ is optionally substituted with 1-5 R³ groups. W is optionally substituted
25 with 1-5 R⁹ groups. Ar² is optionally substituted with 1-5 R³ groups. X is optionally substituted with 1-5 R¹¹ groups. Z is optionally substituted with 1-5 R¹³ groups, and Ar⁴ is optionally substituted with 1-5 R¹⁴ groups.

Y represents an optional linking group between Ar¹ and R² or R³. When m is 0, Y is absent and when m is 1, Y is present. The linking
30 group contains 0-4 carbon atoms and 0-1 heteroatoms selected from O, S and N, and further is optionally substituted with R². Examples of suitable linking groups include: O, S, NR², OCH₂, CH=CH, SO₂CH₂, NHCHMeCH₂, O, CH₂, CH₂CH=CH and the like.

W represents a 3-6 membered linking group containing 0 to 2
35 heteroatoms selected from O, N and S, said linking group optionally containing CO, S(O)_n, C=C or an acetylenic group, and optionally being substituted with R⁹. Examples include OCH₂CH₂, CH=CHCH₂, CH₂SO₂CH₂, NHCHMeCH₂, (CH₂)₅, CH₂CH=CHCH₂, O(CH₂)₃O, CH₂NHCO, CH₂C+C, CH₂OCH₂, CH₂CH=CH, 1,2-c-Pr-CH₂, CH₂-1,2-c-Pr and the like.

5 X represents a linker that is attached to Ar² ortho to the attachment of W. The linker contains 0-4 carbon atoms and not more than one heteroatom selected from O, N and S. Linker X further optionally contains a group CO, S(O)_n, C=C or an acetylenic group, and said linker is optionally substituted with R¹¹. Examples of X include OCH₂, CH=CH,
 10 SO₂CH₂, NHCHMeCH₂O, CH₂, CH₂CH=CH, 1,2-c-Pr, (CH₂)₂O, C+C and the like.

In ZAr⁴, Z represents an optional linker having 0-4 carbon atoms, and being optionally substituted with R¹³. Examples of such a linker include a bond, CH₂CH₂, CH=CH, CHMeCH₂, CH₂, CH₂CH=CH, 1,2-c-Pr, and
 15 the like.

One aspect of the invention that is of particular interest relates to compounds of formula II wherein R¹ is OH, OCH₂Ar³, SCH₂Ar³, OAr³, SAR³ or NR²CH₂Ar³. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest
 20 relates to compounds of formula II wherein Ar³ is an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R³. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest
 25 relates to compounds of formula II wherein Ar² is an aryl or heteroaryl group selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with 1-5 groups selected from R⁴, OR⁴, SR⁴ and halogen.

Another aspect of the invention that is of particular interest
 30 relates to compounds of formula II wherein W is selected from the group consisting of: CH₂OCH₂, (CH₂)₃, CH₂CH=CH, CH=CHCH₂, CH(OH)CH=CH, CH=CHCH(OH), CH₂C+C, C+CCH₂, 1,2-c-Pr-CH₂ and -1,2-c-Pr-CH₂-. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest
 35 relates to compounds of formula II wherein X is selected from the group consisting of: (CH₂)₂, CH=CH, C+C and 1,2-c-Pr. Within this subset, all other variables are as originally defined.

5 Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Q is CO₂H or tetrazole. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Z represents a 0-2 carbon atom
10 linker that is unsubstituted. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Ar⁴ represents an aryl or heteroaryl group selected from the group consisting of benzene, pyridine,
15 thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, said group being optionally substituted with R³. Within this subset, all other variables are as originally defined.

A preferred aspect of the invention relates to compounds represented by formula II wherein:
20 Ar¹ is an aryl or heteroaryl group substituted by R¹ and R³;
R¹ is OH, OCH₂Ar³, SCH₂Ar³, OAr³, SAR³ or NR²CH₂Ar³ ;
Ar³ is selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R³;
25 Ar² represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, and thiazole, said group being optionally substituted with 1-4 members selected from the group consisting of: R⁴, OR⁴, SR⁴ and halogen;
W is selected from the group consisting of: CH₂OCH₂, (CH₂)₃,
30 CH₂CH=CH, CH=CHCH₂, CH(OH)CH=CH, CH=CHCH(OH), CH₂C+C, C+CCH₂, 1,2-c-Pr-CH₂- and -CH₂-1,2-c-Pr-;
X is selected from the group consisting of: (CH₂)₂, CH=CH, C+C and 1,2-c-Pr;
and Q is CO₂H or tetrazole. Within this subset, all other
35 variables are as originally defined.

Another preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar¹ is an aryl or heteroaryl group optionally substituted with R¹ and R³;

5 R^1 is OH, OCH_2Ar^3 , SCH_2Ar^3 , OAr^3 , SAr^3 or $NR_2CH_2Ar^3$;

Ar^3 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^3 ;

10 W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH=CH$, $CH=CHCH_2$, $CH(OH)CH=CH$, $CH=CHCH(OH)$, CH_2C+C or $C+CCH_2$;

Ar^2 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^8 ;

15 X is selected from the group consisting of: $(CH_2)_2$, $CH=CH$, $C+C$ and 1,2-c-Pr;

Q is $CONHSO_2ZAr^4$;

Z is a 0-2 carbon linker and is unsubstituted;

20 Ar^4 is selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, and is optionally substituted by R^3 . Within this subset, all other variables are as originally defined.

A more preferred aspect of the invention relates to compounds represented by formula II wherein:

25 Ar^1 is benzene or thiophene substituted in position 2 and/or position 4 relative to the attachment of W with a member selected from the group consisting of: OH, OCH_2Ar^3 , SCH_2Ar^3 , OAr^3 , SAr^3 and $NR^2CH_2Ar^3$, and is optionally substituted in position 3 with a member selected from the group consisting of: OMe, $OCHF_2$ and lower alkyl;

30 Ar^3 is benzene or thiophene, optionally substituted with R^8 ;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH=CH$, $CH=CHCH_2$, $CH(OH)CH=CH$ and $CH=CHCH(OH)$,

Ar^2 is benzene or thiophene, optionally substituted with 1-4 members selected from R^4 , OR^4 , SR^4 and halogen;

35 X represents a member selected from the group consisting of: $(CH_2)_2$, $CH=CH$ and 1,2-c-Pr, and

Q is CO_2H .

Within this subset, all other variables are as originally defined.

5 Another more preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar¹ is a benzene or a thiophene unsubstituted or substituted in position 2 and/or position 4 relative to the point of attachment to W by a member selected from the group consisting of: OH, OCH₂Ar³, SCH₂Ar³,
10 OAr³, SAr³ and NR²CH₂Ar³; and is optionally substituted at position 3 with one member selected from the group consisting of: OMe, OCHF₂ and lower alkyl;

Ar³ is benzene or thiophene, optionally substituted with R⁸;

W is selected from the group consisting of: CH₂OCH₂, (CH₂)₃,
15 CH₂CH=CH, CH=CHCH₂, CH(OH)CH=CH and CH=CHCH(OH);

Ar² is benzene or thiophene, optionally substituted with R⁴, OR⁴, SR⁴ or halo;

X is selected from the group consisting of: (CH₂)₂, CH=CH and
20 1,2-c-Pr,

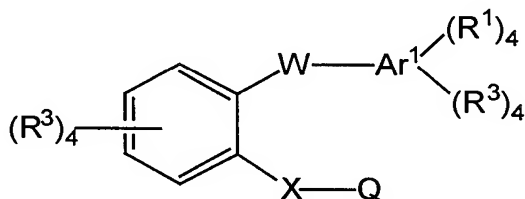
Q is CONHSO₂ZAr⁴,

Z is a bond or CH₂, and

Ar⁴ is selected from the group consisting of: benzene, thiophene, 1,3,4-thiadiazole and naphthalene and is substituted with R⁸.

Within this subset, all other variables are as originally defined.

25 A particularly preferred aspect of the present invention that is of interest relates to compounds represented by formula II':



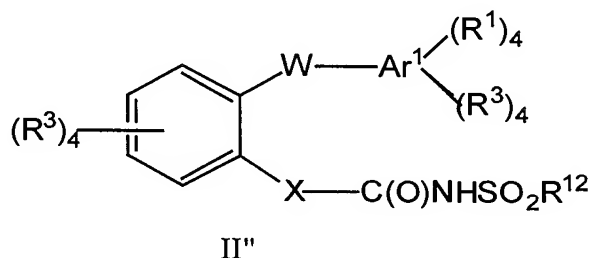
II'

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar¹ represents phenyl, naphthyl, benzofuranyl or
30 methylenedioxyphenyl;

- 5 R^1 represents H, OH, C₁-6alkyl, C₁-6alkoxy, hydroxyC₁-6alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;
 R^3 represents R^4 , halogen, OR⁴ or SR⁴;
 R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF₂
 10 or CF₃;
 X represents a member selected from the group consisting of:
 -(CH₂)₁₋₂-, 1,2-c-Pr-, -CH=CH-, -CH₂O-, -C⁺CCH₂-, -C⁺C-, and -CH₂-C⁺C-;
 W represents a member selected from the group consisting of:
 -(CH₂)₃₋₆-, -CH₂CH=CH-, -CH=CHCH₂-, -CH(OH)CH=CH-,
 15 -CH=CHCH(OH)-, -CH₂-1,2-c-Pr-, -1,2-c-Pr-CH₂-, , -CH₂-O-CH₂-,
 -O-(CH₂)₁₋₃-O-, -CH₂-NHC(O)-, -CF₂CH=CH-, -CH=CHCF₂-, -CH₂CH₂-S-,
 -S-CH₂CH₂-, -CH₂CH₂-SO₂-, -SO₂-CH₂CH₂-, -O-(CH₂)₁₋₃-, -(CH₂)₁₋₃-O-
 and -CH=CHCH₂CH₂-, and
 20 all other variables are as originally defined.

Another particularly preferred aspect of the invention relates to compounds represented by formula II":



- 25 as well as pharmaceutically acceptable salts and hydrates thereof, wherein:
 Ar^1 represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;
 R^1 represents H, OH, C₁-6alkyl, C₁-6alkoxy, hydroxyC₁-6alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl,
 30 haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;
 R^3 represents R^4 , halogen, OR⁴ or SR⁴;

5 R⁴ represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF₂ or CF₃;

X represents a member selected from the group consisting of:
 -(CH₂)₁₋₂-, -1,2-c-Pr-, -CH=CH-, -CH₂O-, -C⁺CCH₂-, -C⁺C-,
 and -CH₂-C⁺C-;

10

W represents a member selected from the group consisting of:
 -(CH₂)₃₋₆-, -CH₂CH=CH-, -CH=CHCH₂-, -CH(OH)CH=CH-,
 -CH=CHCH(OH)-, -CH₂-1,2-c-Pr-, -1,2-c-Pr-CH₂-, -CH₂-O-CH₂-, -O-
 (CH₂)₁₋₃-O-, -CH₂-NHC(O)-, -CF₂CH=CH-, -CH=CHCF₂-, -CH₂CH₂-S-, -S-
 15 CH₂CH₂-, -CH₂CH₂-SO₂-, -SO₂-CH₂CH₂-, -O-(CH₂)₁₋₃-, -(CH₂)₁₋₃-O- and
 -CH=CHCH₂CH₂-, and

R¹² is selected from the group consisting of: C₁₋₆alkyl, thienyl,
 phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl, -CH=CH-phenyl,
 20 said thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl and
 -CH=CH-phenyl groups being optionally substituted with R³.

Examples of compounds within the present application are the
 following:

25

Table I					
(Ar ¹ -W-Ar ² -X-Q)					
Ex	Ar ¹	W	Ar ²	X	Q
1	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	(CH ₂) ₂	CO ₂ H
2	2-(BnO)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
3	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -2- thienyl
4	2-((2-Cl-4-FPh) CH ₂ O)-3-CF ₃ Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
5	2-((2-Cl-4-FPh) CH ₂ O)-3-CF ₃ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
6	2-(BnO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
7	2-(BnO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na

8	4-(BnO)-3,5-(MeO) ₂ Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
9	4-(BnO)-3,5-(MeO) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
10	2-(BnO)-5-AcPh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
11	2-(BnO)-5-AcPh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
12	2-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
13	2-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
14	4-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
15	4-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
16	2-(BnO O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH ₂	CO ₂ Na
17	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH ₂	CO ₂ Na
18	2-(BnO)-3-MePh	CH ₂ CH=CH	5-Cl-1,2-Phe	CH ₂	CO ₂ Na
19	2-(BnO)-3-MePh	CH=CHCH ₂	5-Cl-1,2-Phe	CH ₂	CO ₂ Na
20	4-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	1,2-c-Pr	CO ₂ H
21	2-(BnO)-3-MePh	CH=CHCH ₂	4,5-(MeO) ₂ -1,2-Phe	CH=CH	CO ₂ H
22	2-(BnO)-3-MePh	CH ₂ CH=CH	4,5-(MeO) ₂ -1,2-Phe	CH=CH	CO ₂ H
23	3,4-(methylene dioxy)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
24	3,4-(methylene dioxy)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
25	Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
26	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
27	2-(HO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
28	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
29	2-(BnO)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
30	2-((7-Cl-2-quinolinyl)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
31	2-((7-Cl-2-quinolinyl)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
32	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	bond	CO ₂ H
33	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	bond	CO ₂ Na
34	2-(BnO)-3-MePh	CH ₂ CH=CH	1,2-Phe	bond	CO ₂ Na
35	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ Na
36	2-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ Na
37	4-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ Na

38	4-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
39	4-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
40	3,4-(MeO) ₂ Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
41	3,4-(MeO) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
42	2-(BnO)Ph	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ Na
43	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	(CH ₂) ₂	CONNaSO ₂ -2-thienyl
44	4-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONNaSO ₂ -2-thienyl
45	4-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONNaSO ₂ -2-thienyl
46	2-(BnO)-3-MePh	CH ₂ -1,2-c-Pr	1,2-Phe	CH=CH	CO ₂ Na
47	2-(BnO)-3-MePh	1,2-c-Pr-CH ₂	1,2-Phe	CH=CH	CO ₂ Na
48	2-(BnO)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ Na
49	2-(BnO)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
50	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
51	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ H
52	2-((4-FPh)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
53	2-((4-FPh)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
54	2-((3,4-F ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
55	2-((3,4-F ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
56	2-((3,5-F ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
57	2-((3,5-F ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
58	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
59	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
60	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
61	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
62	2-((4-CF ₃ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H

63	2-((4-CF ₃ Ph) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
64	2-((4- (CHF ₂ O)Ph) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
65	2-((4-(CHF ₂ O) Ph)CH ₂ O)-3- MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
66	2-((4-CF ₃ Ph) CH ₂ O)-3- (HOCH ₂)Ph	CH=CHCH(O H)	1,2-Phe	CH=CH	CO ₂ H
67	2-((4-CF ₃ Ph) CH ₂ O)-3- (HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
68	2-((4-CF ₃ Ph) CH ₂ O)-3-MePh	CH=CHCH(O H)	1,2-Phe	CH=CH	CO ₂ H
69	2-(PhCH ₂ O)-3- (HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
70	3-(PhO)Ph	CH ₂ OCH ₂	1,2-Phe	CH=CH	CO ₂ Na
71	2-(PhO)Ph	CH ₂ OCH ₂	1,2-Phe	CH=CH	CO ₂ Na
72	3-(BnO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
73	3-(BnO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
74	2-(BnO)Ph	O(CH ₂) ₃ O	1,2-Phe	CH=CH	CO ₂ Na
75	2-(PhCHMeO)-3 -MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
76	2-(PhCHMeO)-3 -MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
77	3-(PhO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
78	3-(PhO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
79	3-Ph benzofuran-7-yl	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ Na
80	3-Ph benzofuran-7-yl	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ Na
81	Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
82	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
83	4-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -2- thienyl
84	4-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -2- thienyl
85	2-(BnO)-1- naphthyl	CH ₂ NHCO	1,2-Phe	CH=CH	CO ₂ H
86	2-((2-Cl-4-FPh) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
87	2-((2-Cl-4-FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H

88	2-((2,4-F ₂ Ph) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
89	2-((2,4-F ₂ Ph) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
90	2-((2,4,6-F ₃ Ph) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
91	2-((2,4,6-F ₃ Ph) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
92	2-((2,6-Cl ₂ -4- FPh) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
93	2-((2,6-Cl ₂ -4- FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
94	2-((2,4- F ₂ Ph)CH ₂ O) -3-(CHF ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
95	2-((2,4-F ₂ Ph) CH ₂ O) -3-(CHF ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
96	2-((4-FPh)CH ₂ O) -3-MePh	CF ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
97	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCF ₂	1,2-Phe	CH=CH	CO ₂ H
98	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -(4-i- PrPh)
99	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -(4-t- BuPh)
100	2-((4-FPh)CH ₂ O) -3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -(4- (MeO)Ph)
101	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2,3-Cl ₂ Ph)
102	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCH ₂	4-Cl-1,2-Phe	CH=CH	CONHSO ₂ -(5- Br-2-(MeO)Ph)
103	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₂ S	3-F-1,2-Phe	CH=CH	CONHSO ₂ -(2,3,4-Cl ₃ Ph)
104	2-((4-FPh) CH ₂ O)-3-MePh	(CH ₂) ₂ S	6-CF ₃ -1,2- Phe	CH=CH	CONHSO ₂ -(5- F-2-MePh)
105	2-((4-FPh) CH ₂ O)-3-MePh	(CH ₂) ₂ S	4,5-F ₂ -1,2- Ph	CH=CH	CONHSO ₂ -(2,5-Me ₂ Ph)
106	2-((4-FPh) CH ₂ O)-3-MePh	(CH ₂) ₂ SO ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4- CF ₃ Ph)
107	2-((4-FPh) CH ₂ O)-3-MePh	(CH ₂) ₂ SO ₂	1,2-Phe	CH=CH	CONHSO ₂ -2- naphthyl
108	2-((4-FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	3-F-1,2-Phe	CH=CH	CONHSO ₂ -(3- Cl-4-FPh)

109	2-((4-FPh) CH ₂ O)-3-MePh	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4- n-PrPh)
110	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2- ClPh)
111	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4- FPh)
112	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	S(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2- PhPh)
113	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	S(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2- CF ₃ Ph)
114	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	S(CH ₂) ₂	4-t-Bu-1,2- Phe	CH=CH	CONHSO ₂ -(4- Cl-2,5-Me ₂ Ph)
115	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2,5-Cl ₂ Ph)
116	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4- Br-2-(CF ₃ O)Ph)
117	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(CH ₂ Ph)
118	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	(CH ₂) ₂ O	1,2-Phe	CH=CH	CONHSO ₂ -(1- naphthyl)
119	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	(CH ₂) ₂ O	4,5-F ₂ -1,2- Phe	CH=CH	CONHSO ₂ -(2- FPh)
120	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	(CH ₂) ₂ O	1,2-Phe	CH=CH	CONHSO ₂ -(2,4-Cl ₂ Ph)
121	2-((4-FPh) CH ₂ O)-3- (MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -(CH=CHPh)
122	2-((4- FPh)CH ₂ O)-3- (MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -((3,5-(CF ₃) ₂ Ph)
123	2-((4- FPh)CH ₂ O)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -((2,5-Cl ₂ -3- thienyl)
124	2-((4-FPh) CH ₂ O)Ph	(CH ₂) ₄	3-F-1,2-Phe	CH=CH	CONHSO ₂ -(3- BrPh)
125	2-((4-FPh) CH ₂ O)Ph	(CH ₂) ₄	3-MeO-1,2- Phe	CH=CH	CONHSO ₂ -(2- BrPh)

126	2-((4-FPh) CH ₂ O)Ph	(CH ₂) ₄	1,2-Phe	CH=CH	CONHSO ₂ -(2- NO ₂ Ph)
127	2-((4-FPh) CH ₂ O)Ph	(CH ₂) ₅	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(3- ClPh)
128	2-((4-FPh) CH ₂ O)Ph	(CH ₂) ₅	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4- (CF ₃ O)Ph)
129	2-HOPh	CH=CH(CH ₂) ₂	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -8- quinolinyl
130	2-((4-FPh) CH ₂ O)Ph	CH=CH(CH ₂) ₂	5-(CF ₃ O)- 1,2-Phe	(CH ₂) ₂	CONHSO ₂ - (3,4-Cl ₂ Ph)
131	4-((2,6-Cl ₂ -4- FPh)CH ₂ O)-3- MePh	CH=CH(CH ₂) ₂	3-F-1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4- EtPh)
132	2-((4-FPh) CH ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4- Cl-2-NO ₂ Ph)
133	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	4,5-F ₂ -1,2- Phe	CH=CH	CONHSO ₂ -(2- Cl-3-Br-5- thienyl)
134	2-((4-FPh) CH ₂ O)Ph	CH ₂ CH=CH	4,5-F ₂ -1,2- Phe	CH=CH	CONHSO ₂ - (3,4-(MeO) ₂ Ph)
135	2-HOPh	CH=CHCH ₂	4,5-F ₂ -1,2- Phe	CH=CH	CONHSO ₂ - (2,5-Cl ₂ -3-Br-4- thienyl)
136	4-((4-FPh)CH ₂ O)- 3-(MeO)Ph	CH ₂ CH=CH	4,5-F ₂ -1,2- Phe	CH=CH	CONHSO ₂ -(4- Br-2,5-F ₂ Ph)
137	4-((4-FPh)CH ₂ O)- 3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(5- (AcNH)-1,3,4- thiadiazol-2-yl)
138	4-((4-FPh) CH ₂ O)-3- (MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ - (2,3,4,5,6- F ₅ Ph)
139	4-((2-Cl-4-FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2- CNPh)
140	2-((4-FPh) CH ₂ O)Ph	CH ₂ CH=CH	4-F-1,2-Phe	CH=CH	CONHSO ₂ -(2- Cl-6-MePh)
141	2-HOPh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ - (2,4,6-Me ₃ Ph)
142	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ - (2,3-Br ₂ -2- thienyl)
143	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH ₂ O	CONHSO ₂ -(4- NO ₂ Ph)
144	2-((4-FPh) CH ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	CH ₂ O	CONHSO ₂ - (3,5-Cl ₂ Ph)
145	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	prop-1-yne- 1,3-diyl	CONHSO ₂ -(5- Cl-2-thienyl)

146	4-((2,4-F ₂ Ph) CH ₂ O)-3- (MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH ₂ O	CONHSO ₂ -(4- CF ₃ Ph)
147	2-HO-3-MePh	CH=CHCH ₂	1,2-Phe	CH ₂ O	CONHSO ₂ - (2,4-F ₂ Ph)
148	2-((4-FPh) CH ₂ O)Ph	CH ₂ CH=CH	4-F-1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -(4- ClPh)
149	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -(3- CF ₃ Ph)
150	4-HOPh	CH ₂ CH=CH	1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -Ph
151	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	prop-2-yne- 1,3-diyl	CONHSO ₂ -(5- Br-2-thienyl)
152	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH ₂ CH=CH	1,2-Phe	1,2- ethynediyl	CONHSO ₂ -Me
153	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	CONHSO ₂ - (2,5-(MeO) ₂ Ph)
154	6-((4-FPh) CH ₂ O)-2- naphthyl	CH ₂ CH=CH	4-F-1,2-Phe	1,2-c-Pr	CONHSO ₂ -(3- MePh)
155	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	CONHSO ₂ -(4- MePh)
156	4-HO-3- (MeO)Ph	CH ₂ CH=CH	1,2-Phe	1,2-c-Pr	CONHSO ₂ -n- Bu
157	4-((4-FPh)CH ₂ O) -1-naphthyl	CH=CHCH ₂	1,2-Phe	1,2-c-Bu	CONHSO ₂ -(2- Cl-4-FPh)
158	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ - (2-MePh)
159	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ - c-Pr
160	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
161	4-((2,4-F ₂ Ph) CH ₂ O)-3- (MeO)Ph	(CH ₂) ₃	4-F-1,2-Phe	CH=CH	1H-tetrazol- 5-yl
162	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	3-MeO- 1,2-Phe	CH=CH	1H-tetrazol- 5-yl
163	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	1H-tetrazol- 5-yl
164	4-HO-3- (MeO)Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	1H-tetrazol- 5-yl
165	Ph	CH=CHCH ₂	1,2-Phe	(CH ₂) ₂	1H-tetrazol- 5-yl
166	2-((4-FPh)CH ₂ O) -3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	SO ₃ H
167	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	4-F-1,2-Phe	(CH ₂) ₂	SO ₃ H

5 Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

15 Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc salts, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred

- 5 are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula II are meant to also include the pharmaceutically acceptable salts and hydrates.

10

Dose Ranges

- The magnitude of a prophylactic or therapeutic dose of a compound of Formula II will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of Formula II and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

- The active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from as low as about 0.5 mg to as high as about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage units will generally contain between from about 1 mg to about 2 g of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

Pharmaceutical Compositions

- The pharmaceutical compositions of the present invention comprise a compound of Formula II as an active ingredient or a pharmaceutically acceptable salt or hydrate, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

5 For the treatment of any of the prostanoid mediated diseases
compound II may be administered orally, topically, parenterally, by inhalation
spray or rectally in dosage unit formulations containing conventional non-toxic
pharmaceutically acceptable carriers, adjuvants and vehicles. The term
parenteral as used herein includes subcutaneous injections, intravenous,
10 intramuscular, intrasternal injection or infusion techniques. In addition to the
treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep,
dogs, cats, etc., the compound of the invention is effective in the treatment of
humans.

 The pharmaceutical compositions containing the active
15 ingredient may be in a form suitable for oral use, for example, as tablets,
troches, lozenges, aqueous or oily suspensions, dispersible powders or
granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions
intended for oral use may be prepared according to any method known to the
art for the manufacture of pharmaceutical compositions and such
20 compositions may contain one or more agents selected from the group
consisting of sweetening agents, flavouring agents, colouring agents and
preserving agents in order to provide pharmaceutically elegant and palatable
preparations. Tablets contain the active ingredient in admixture with non-
toxic pharmaceutically acceptable excipients which are suitable for the
25 manufacture of tablets. These excipients may be for example, inert diluents,
such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or
sodium phosphate; granulating and disintegrating agents, for example, corn
starch, or alginic acid; binding agents, for example starch, gelatin or acacia,
and lubricating agents, for example, magnesium stearate, stearic acid or talc.
30 The tablets may be uncoated or they may be coated by known techniques to
delay disintegration and absorption in the gastrointestinal tract and thereby
provide a sustained action over a longer period. For example, a time delay
material such as glyceryl monostearate or glyceryl distearate may be
employed. They may also be coated by the technique described in the U.S.
35 Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic
tablets for control release.

 Formulations for oral use may also be presented as hard gelatin
capsules wherein the active ingredient is mixed with an inert solid diluent, for
example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin

- 5 capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such
10 excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty
15 acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as
20 polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or
25 aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl
30 alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an
35 aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional

- 5 excipients, for example sweetening, flavouring and colouring agents, may also be present.

 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid
10 paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The
15 emulsions may also contain sweetening and flavouring agents.

 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile
20 injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for
25 example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this
30 purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

 Compound II may also be administered in the form of suppositories for rectal administration of the drug. These compositions can
35 be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

5 For topical use, creams, ointments, gels, solutions or
suspensions, etc., containing the compound of Formula II are employed. (For
purposes of this application, topical application shall include mouth washes
and gargles.) Topical formulations may generally be comprised of a
pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer,
10 preservative system, and emollient.

 The composition of the present invention may also include
additional therapeutic agents. For example, conventional analgesics such as
aspirin or acetaminophen may be incorporated into the composition. Other
examples of additional therapeutic agents which can be included are NSAIDs,
15 such as ibuprofen or naproxen, COX-2 selective compounds, such as those
which are described in the following patents and published applications:
WO96/25405, U.S.Pat. No. 5,633,272, WO97/38986, U. S. Pat. No.
5,466,823, WO98/03484, WO97/14691 and WO95/00501, and other
compounds.

20 Utilities

 The ability of the compounds of Formula II to interact with
prostaglandin receptors makes them useful for preventing or reversing
undesirable symptoms caused by prostaglandins in a mammalian, especially
25 human, subject. This mimicking or antagonism of the actions of
prostaglandins indicates that the compounds and pharmaceutical
compositions thereof are useful to treat, prevent, or ameliorate in mammals
and especially in humans: Pain, fever and inflammation of a variety of
conditions including rheumatic fever, symptoms associated with influenza or
30 other viral infections, common cold, low back and neck pain, skeletal pain,
post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains
and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid
arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing
spondylitis, bursitis, burns including radiation and corrosive chemical injuries,
35 sunburns, pain following surgical and dental procedures as well as immune
and autoimmune diseases. In addition, such a compound may inhibit cellular
neoplastic transformations and metastatic tumor growth and hence can be
used in the treatment of cancer. Compounds of formula II is also of use in the

5 treatment and/or prevention prostaglandin-mediated proliferation disorders such as may occur in diabetic retinopathy and tumor angiogenesis.

Compounds of formula II inhibit prostanoid-induced smooth muscle contraction by antagonizing contractile prostanoids or mimicking relaxing prostanoids and hence may be use in the treatment of
10 dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, the treatment of glaucoma, for the prevention of bone loss (treatment of osteoporosis) and for the promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

15 By virtue of its prostanoid or prostanoid antagonist activity, compound II are useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contraindicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a
20 recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; thrombosis, occlusive vascular diseases; those prior to surgery or taking anti-coagulants. Compound II will also be useful as a cytoprotective agent for patients undergoing
25 chemotherapy.

Consequently one aspect of the invention addresses a method of treating or preventing a prostaglandin mediated disease in a mammalian patient in need thereof, comprising administering to said patient a compound in accordance with formula II in an amount which is effective for treating or
30 preventing said prostaglandin mediated disease.

In another aspect of the invention, a method of treating or preventing a prostaglandin mediated disease is described which is further comprised of administering to said patient an effective amount of a COX-2 selective inhibiting compound.

35 More particularly, a method of treating or preventing a prostaglandin mediated disease is addressed wherein the prostaglandin mediated disease is selected from the group consisting of:

pain, fever, inflammation, rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and

5 neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache,
migraine, toothache, sprains, strains, myositis, neuralgia, synovitis, arthritis
including rheumatoid arthritis, degenerative joint diseases (osteoarthritis),
gout, ankylosing spondylitis, bursitis, burns including radiation and corrosive
10 chemical injuries, sunburns, pain following surgical and dental procedures,
immune and autoimmune diseases, cellular neoplastic transformations,
metastatic tumor growth, prostaglandin-mediated proliferation disorders such
as diabetic retinopathy and tumor angiogenesis, dysmenorrhea, premature
labor, asthma, eosinophil related disorders, Alzheimer's disease, glaucoma,
bone loss (osteoporosis), promotion of bone formation (treatment of fractures)
15 and other bone diseases such as Paget's disease.

Further, a method of treating or preventing an E type
prostaglandin mediated disease in a mammalian patient is described herein,
comprising administering to said patient an amount of an E type
prostaglandin ligand in an amount which is effective to treat or prevent said E
20 type prostaglandin mediated disease.

More particularly, the method described with respect to E-type
prostaglandin mediated diseases further comprises administering a COX-2
selective inhibitor.

Examples of COX-2 selective compounds are such as those
25 described in the following patents and published applications: WO96/25405,
U.S.Pat. No. 5,633,272, WO97/38986, U. S. Pat. No. 5,466,823,
WO98/03484, WO97/14691 and WO95/00501.

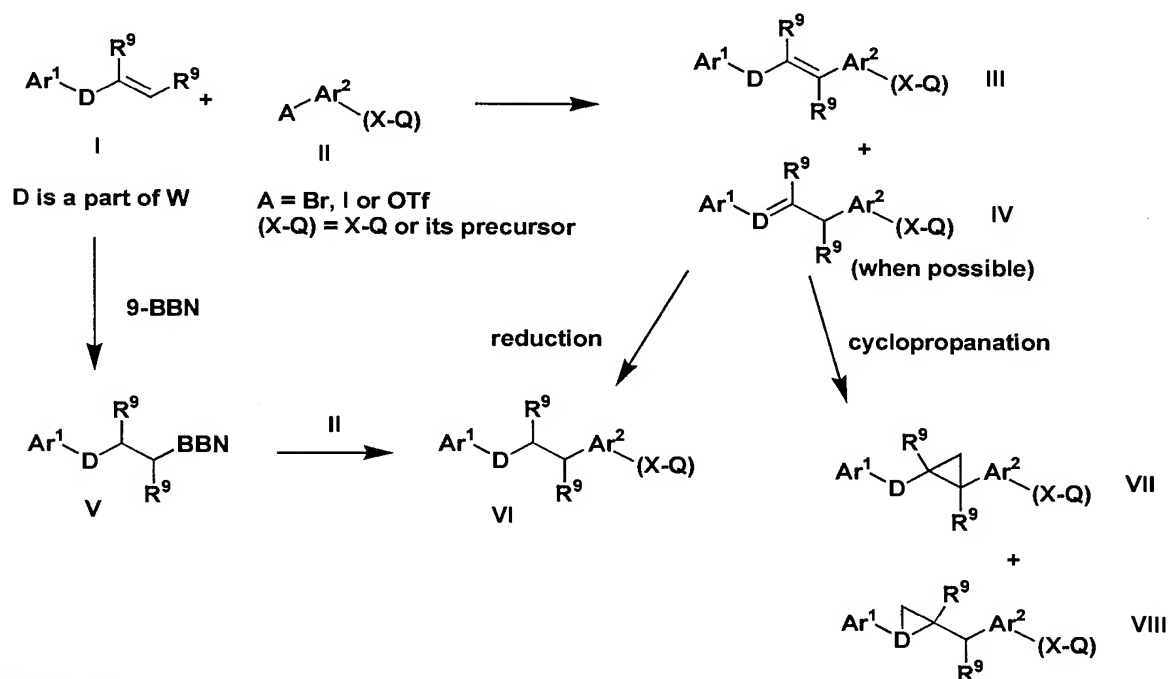
METHODS OF SYNTHESIS

30 Compounds of the present invention can be prepared according
to the following methods. Methods A, I and J showed how to form the linker
W between Ar¹ and Ar²; methods B and E - H concentrate on linker X; method
C explained how to obtain sulfonamides and method D illustrate how to
substitute Ar¹. One particular method is usually used in conjunction with
35 other methods to yield compounds of formula II. Reagents given below are
for illustration of the chemistry only and should not be limiting this patent:
other reagents might be as effective or better for each reaction described.

Method A

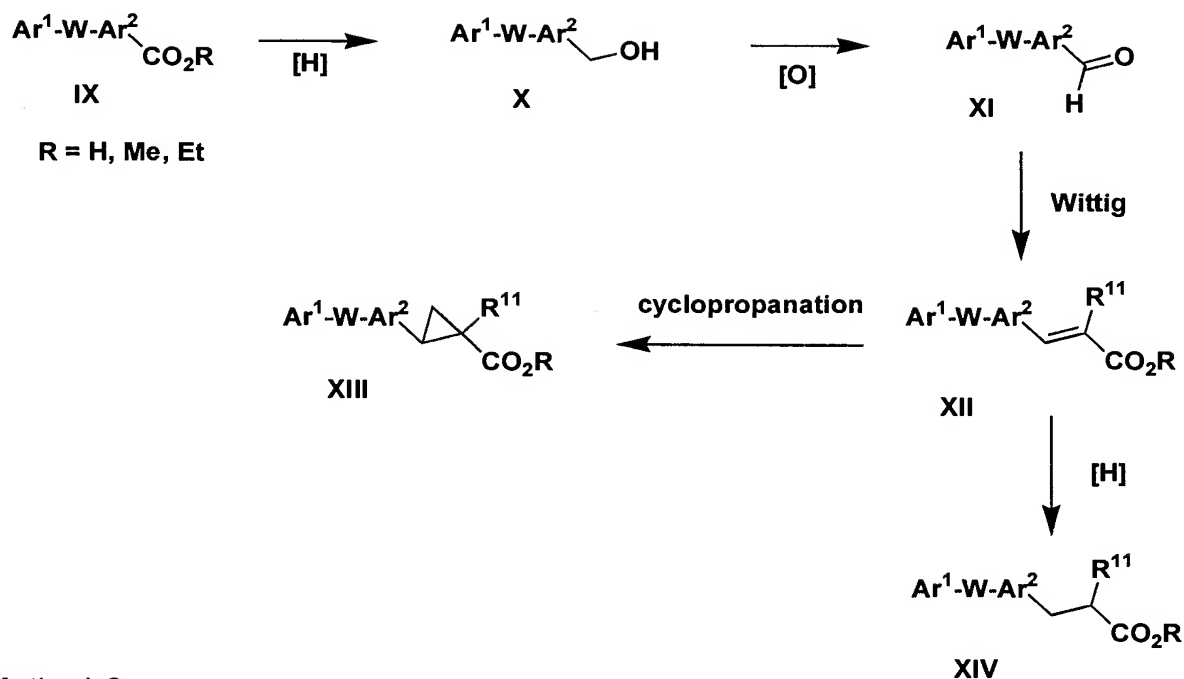
- 5 An aryl alkene I can be coupled with an aryl bromide, iodide or triflate II in the presence of a catalyst such as $\text{Pd}(\text{OAc})_2$ to give the two isomers III and IV. Catalytic hydrogenation of the double bond, using Pd/C or $(\text{Ph}_3\text{P})_3\text{RhCl}$, yield the compound VI. Alternatively, VI can be prepared from I via formation of the boronate V with 9-borabicyclo[3.3.1]nonane and coupling with II in the presence of a catalyst such as $\text{PdCl}_2(\text{dppf})$. Cyclopropanation of the alkenes III and IV can be performed using conditions such as $\text{CH}_2\text{N}_2/\text{PdOAc}_2$ to give VII and VIII. The group X-Q in compounds III, IV, VI, VII and VIII can then be transformed to another X-Q group to afford other
- 10 substructures of II.

15



Method B

- The acid or esters IX can be reduced to the alcohol X using reagents such as diisobutylaluminum hydride or sodium borohydride.
- 20 Oxidation to the aldehyde XI can be performed using MnO_2 or pyridinium chlorochromate. Wittig reaction on XI afford the propenoate XII which can be cyclopropanated ($\text{CH}_2\text{N}_2/\text{Pd}(\text{OAc})_2$) to XIII or reduced ($\text{H}_2/\text{Pd/C}$) to XIV. When R = H, compounds IX, XII, XIII and XIV are substructures of II.

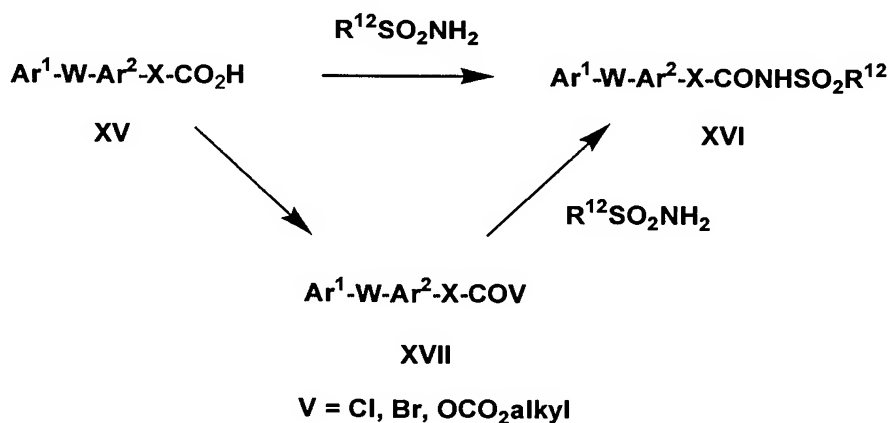


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Method C

The acid XV, which is a substructure of II, can be transformed to the sulfonamide XVI, another substructure of II, by treatment with a sulfonamine in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Another method for the preparation of XVI involves the formation of an acid chloride or a mixed anhydride XVII and reaction with the sulfonamine in the presence of a base such as Et₃N.

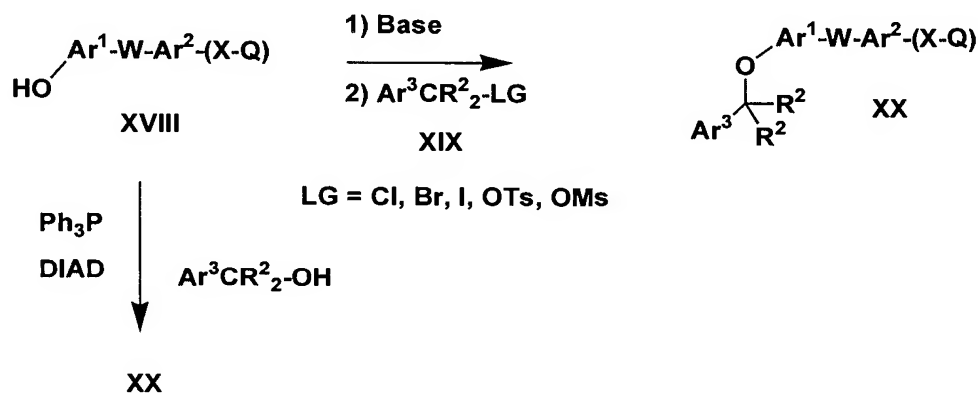
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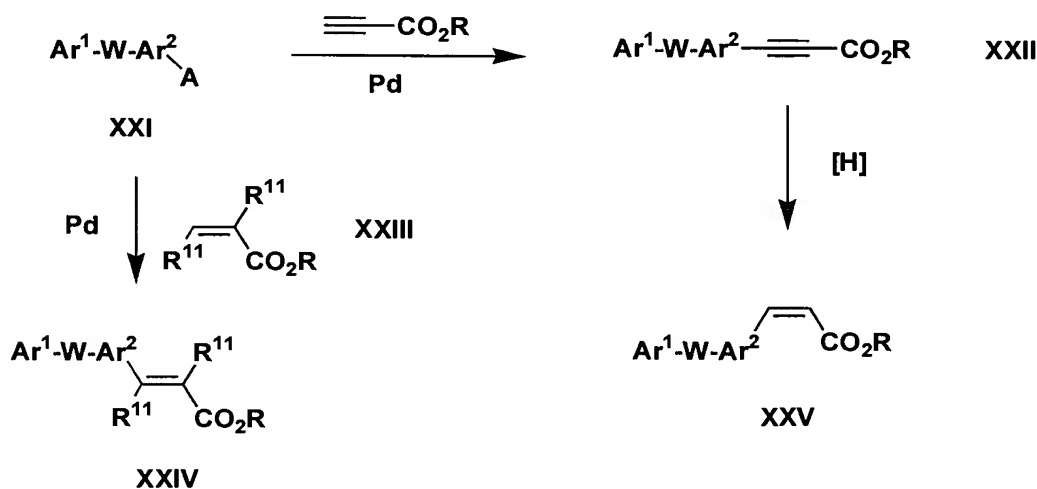
Method D

- 5 When compound II or its precursor is substituted by an hydroxyl group as in XVIII, it can be alkylated by a reagent containing a leaving group XIX in the presence of a base such as NaH or DBU to yield the ether XX. Alternatively, Mitsunobu reaction with the alcohol derivative of XIX also yield XX. The group X-Q in XX can then be transformed to another X-Q group to afford another example of II.
- 10



Method E

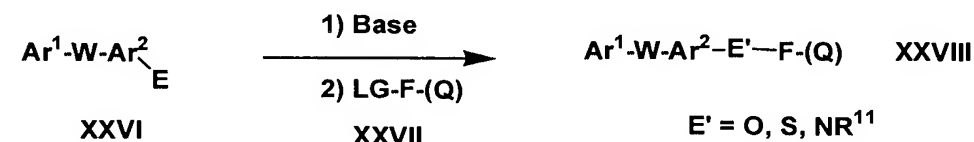
- 15 The aryl bromide, iodide or triflate XXI can be coupled with an alkyne or the alkene XXIII in the presence of a catalyst such as Pd(OAc)₂ (J. Org. Chem. 1979, 4078) to give the products XXII or XXIV respectively. Catalytic hydrogenation of the alkyne XXII over Lindlar's catalyst can afford the cis alkene XXV. When R = H, compounds XXII, XXIV and XXV are
- 20 substructures of II and they can be treated as in method B to yield other examples of II.



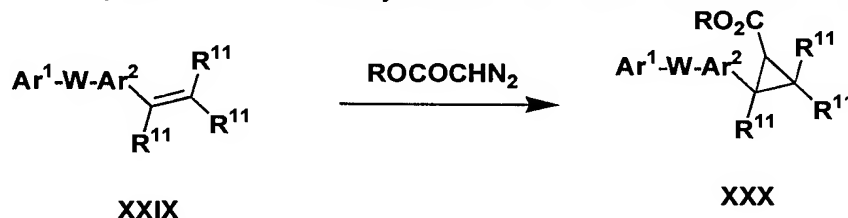
5

Method F

An aryl thiol, alcohol or amine XXVI can be treated with a base and then with reagent XXVII to yield the derivative XXVIII. The group E'-F-Q can be transformed to another E'-F-Q group using the other methods described here and yield examples of II possessing an heteroatom attached to Ar² in the linker X.

E = OH, SH, NHR¹¹F is a part of X
(Q) is Q or its precursor15 Method G

Compounds II possessing a cyclopropane unit as an X group XXX can be synthesized via a reaction between the alkene XXIX and a diazoacetate in the presence of a catalyst such as rhodium acetate dimer.

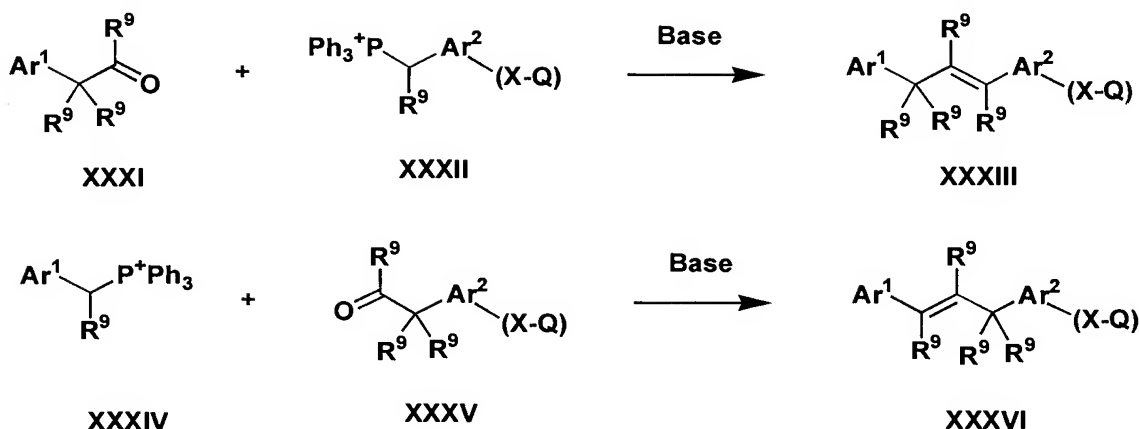


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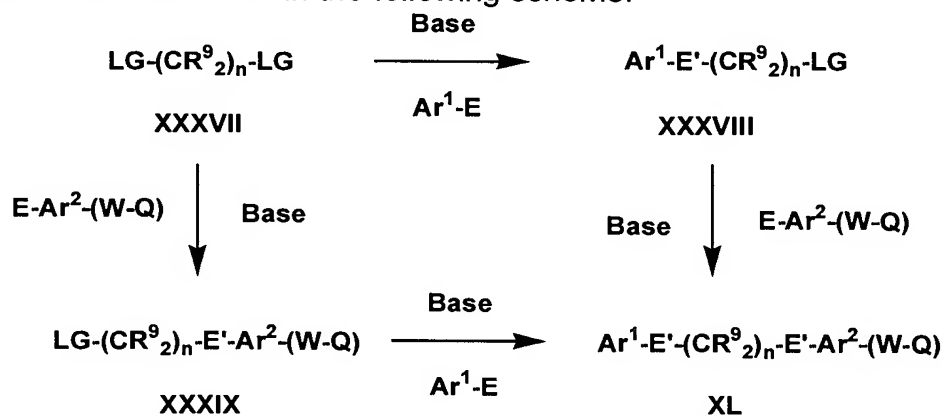
Method H

Compounds II possessing a double bond as part of the linker X can be synthesized via a Wittig reaction as exemplified in the next scheme. Phosphonium salts XXXII and XXXIV can be obtained from the corresponding Ar-CHR⁹-LG by reaction with Ph₃P.

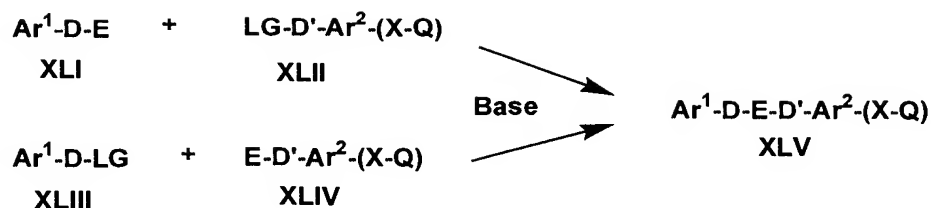
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Method I

Compounds II possessing two heteroatoms as part of the linker W as in XL can be synthesized from a reagent containing two leaving groups XXXVII and two aromatics compounds containing an alcohol, an amine or a thiol function E as described in the following scheme.

Method J

Compounds II possessing one heteroatom as part of the linker W as in XLV can be synthesized from a reagent containing one leaving group XLII or XLIII and an aromatic compound containing an alcohol, an amine or a thiol function E (XLI or XLIV) as described in the following two equations.



5

D and D' are part of W

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compound of Formula II can be tested using the following assays to determine their prostanoid antagonist or agonist activity *in vitro* and *in vivo* and their selectivity. The prostaglandin receptors investigated were DP, EP₁, EP₂, EP₃, EP₄, FP, IP and TP.

Stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293(ebna) cell line

Prostanoid receptor cDNAs corresponding to full length coding sequences were subcloned into the appropriate sites of mammalian expression vectors and transfected into HEK 293(ebna) cells. HEK 293(ebna) cells expressing the individual cDNAs were grown under selection and individual colonies were isolated after 2-3 weeks of growth using the cloning ring method and subsequently expanded into clonal cell lines.

Prostanoid receptor binding assays

HEK 293(ebna) cells are maintained in culture, harvested and membranes are prepared by differential centrifugation, following lysis of the cells in the presence of protease inhibitors, for use in receptor binding assays. Prostanoid receptor binding assays are performed in 10 mM MES/KOH (pH 6.0) (EPs, FP and TP) or 10 mM HEPES/KOH (pH 7.4) (DP and IP), containing 1 mM EDTA, 10 mM divalent cation and the appropriate radioligand. The reaction is initiated by addition of membrane protein. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. Non-specific binding is determined in the presence of 1 μ M of the corresponding non-radioactive prostanoid. Incubations are conducted for 60 min at room temperature or 30 °C and terminated by rapid filtration. Specific binding is calculated by subtracting non specific binding from total

5 binding. The residual specific binding at each ligand concentration is calculated and expressed as a function of ligand concentration in order to construct sigmoidal concentration-response curves for determination of ligand affinity.

10 Prostanoid receptor agonist and antagonist assays

Whole cell second messenger assays measuring stimulation (EP₂, EP₄, DP and IP in HEK 293(ebna) cells) or inhibition (EP₃ in human erythroleukemia (HEL) cells) of intracellular cAMP accumulation or mobilization of intracellular calcium (EP₁, FP and TP in HEK 293(ebna) cells stably transfected with apo-aequorin) are performed to determine whether receptor ligands are agonists or antagonists. For cAMP assays, cells are harvested and resuspended in HBSS containing 25 mM HEPES, pH 7.4. Incubations contain 100 µM RO-20174 (phosphodiesterase type IV inhibitor, available from Biomol) and, in the case of the EP₃ inhibition assay only, 15 µM forskolin to stimulate cAMP production. Samples are incubated at 37 C for 10 min, the reaction is terminated and cAMP levels are then measured. For calcium mobilization assays, cells are charged with the co-factors reduced glutathione and coelenterazine, harvested and resuspended in Ham's F12 medium. Calcium mobilization is measured by monitoring luminescence provoked by calcium binding to the intracellular photoprotein aequorin. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. For agonists, second messenger responses are expressed as a function of ligand concentration and both EC₅₀ values and the maximum response as compared to a prostanoid standard are calculated. For antagonists, the ability of a ligand to inhibit an agonist response is determined by Schild analysis and both K_B and slope values are calculated.

Rat Paw Edema Assay

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, (1995)).

LPS-Induced Pyrexia in Conscious Rats

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, (1995)).

5 LPS-Induced Pyrexia in Conscious Squirrel Monkeys

The method is the same as described in Chan *et al* (Eur. J. Pharmacol. 327: 221- 225, (1997)).

Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

10 The method is the same as described in Boyce *et al* (Neuropharmacology 33: 1609-1611, (1994)).

Adjuvant-Induced Arthritis in Rats

Female Lewis rats (body weight ~146-170 g) were weighed, ear
15 marked, and assigned to groups (a negative control group in which arthritis
was not induced, a vehicle control group, a positive control group
administered indomethacin at a total daily dose of 1 mg/kg and four groups
administered with a test compound at total daily doses of 0.10-3.0 mg/kg)
such that the body weights were equivalent within each group. Six groups of
20 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium*
butyricum in 0.1 mL of light mineral oil (adjuvant), and a negative control
group of 10 rats was not injected with adjuvant. Body weights, contralateral
paw volumes (determined by mercury displacement plethysmography) and
lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were
25 determined before (day -1) and 21 days following adjuvant injection, and
primary paw volumes were determined before (day -1) and on days 4 and 21
following adjuvant injection. The rats were anesthetized with an
intramuscular injection of 0.03 - 0.1 mL of a combination of Ketamine (87
mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant.
30 The radiographs were made of both hind paws on day 0 and day 21 using the
Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were
developed in an automatic processor. Radiographs were evaluated for
changes in the soft and hard tissues by an investigator who was blinded to
experimental treatment. The following radiographic changes were graded
35 numerically according to severity: increased soft issue volume (0-4),
narrowing or widening of joint spaces (0-5) subchondral erosion (0-3),
periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative
joint changes (0-3). Specific criteria were used to establish the numerical
grade of severity for each radiographic change. The maximum possible score
40 per foot was 26. A test compound at total daily doses of 0.1, 0.3, 1, and 3

5 mg/kg/day, indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

10

EXAMPLES

The invention is further illustrated in the following non-limiting examples in which, unless otherwise stated:

15 yields are given for illustration only and are not necessarily the maximum attainable;

all the end products of the formula II were analyzed by NMR, TLC and mass spectrometry;

20 intermediates were all analyzed by NMR and TLC; most compounds were purified by flash chromatography on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid) with a solvent such as ether:hexane 1:1;

the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; temperatures are in degrees Celsius.

25

EXAMPLE 1

3-(2-(3-(2-(BENZYLOXY)-3-METHYLPHENYL)PROPYL)PHENYL)PROPANOIC ACID

30 A mixture of the products of examples 28 and 29 was dissolved in 2 ml MeOH:EtOAc 1:1 with *tris*(triphenylphosphine)rhodium(I) chloride (2mg) and the mixture hydrogenated under 60 psi of H₂. The reaction was followed by mass spectroscopy and, when completed, the solvent was evaporated and the product purified by flash chromatography with EtOAc:toluene containing 1% AcOH.

35 MS (APCI, neg.) 387.2 (M-1), 279.2.

- 5 0.5 N HCl, dried over Na₂SO₄ and concentrated to dryness. Recrystallization from ether:hexane afforded the title product as a white solid. Yield: 251 mg, 62%.

¹H NMR (Acetone-d₆) δ 3.68 and 3.74 (2H, 2d), 5.10 and 5.20 (2H, 2s), 6.30 - 6.53 (2H, m), 6.70 - 6.93 (2H, m), 7.03 (1H, 2d), 7.18 (1H, m),
10 7.25 - 7.43 (7H, m), 7.50 (2H, m), 7.68 and 7.77 (1H, 2d), 8.03 (1H, 2d).

Step 3

- The acids of step 2 were dissolved in EtOH and 1.0 equiv. of NaOH 1.0 N was added. The solvent was evaporated, the oil dissolved in
15 water and the products were freeze-dried to afford a white solid.
MS (APCI, neg.) 369.0 (M-1)

- The products of the following examples have been prepared in a manner similar to examples 6 and 7 and are mixtures of 2 compounds
20 each.

Examples	Note	MS (APCI, neg.) ^c
8 & 9		429.1
10 & 11	d	411.2
12 & 13		399.1
14 & 15		399.1
16 & 17	a	371.1, 327.2 (M-CO ₂ H)
18 & 19	a	405.2, 361.0 (M-CO ₂ H)
21 & 22	d	443.1
23 & 24	d	307.1
25 & 26	d	263.1, 219.1 (M-CO ₂ H)
28 & 29	b	383.2
38 & 39	d	293.1, 234.0
40 & 41	d	323.1, 264.1
72 & 73		368.9, 233.2

- a) Pd coupling (step 2) at 120°C o.n.,
b) the two products were separated by HPLC on a NovaPak C18 column,
25 c) M-1
d) the sodium salt was not prepared

5

EXAMPLE 20
2-(2-(3-(4-(BENZYLOXY)-3-
METHOXYPHENYL)PROPYL)PHENYL)CYCLOPROPANE
CARBOXYLIC ACID

10 Step 1 (E)-2-(2-(3-(4-(benzyloxy)-3-methoxyphenyl)propyl)phenyl)-2-propenoic acid

A solution of 9-borabicyclo[3.3.1]nonane 0.5 M in THF (3.8 ml, 1.5 equiv.) was added slowly to 4-allyl-1-benzyloxy-2-methoxybenzene (257 mg, 1.21 mmol, prepared as in examples 6 and 7, step 1) and the mixture was stirred at r.t. for 30 min. K₃PO₄ (384 mg), 2-bromocinnamic acid (222 mg, 978 mmol), (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II) (31 mg) and DMF (4 ml) were added and the mixture was degassed and stirred at 50°C o.n.. A saturated solution of NH₄Cl was added, the solution was acidified with AcOH and the product was extracted in EtOAc, dried over Na₂SO₄ and partially purified by flash chromatography with EtOAc:toluene:AcOH 5:95:1.

Step 2 Methyl 2-(2-(3-(4-(benzyloxy)-3-methoxyphenyl)propyl)phenyl)cyclopropane-carboxylate

25 The acid of step 1 was treated with diazomethane in ether at reflux. The solvent was removed and the ester was purified by flash chromatography with EtOAc:toluene 2.5:97.5.

Step 3

30 The ester of step 2 was hydrolyzed with NaOH as in example 61, step 3. The final product was purified by HPLC with EtOAc:toluene:AcOH 2.5:97.5:1 on a μ Porasil column to yield the title cyclopropaneacetic acid.

¹H NMR (acetone, d₆) δ 1.43 (2H, m), 1.76 (1H, m), 1.93 (2H, m), 2.55 (1H, m), 2.65 (2H, t), 2.82 (2H, m), 3.80 (3H, s), 5.07 (2H, s), 6.72 (1H, d), 6.87 (1H, s), 6.91 (1H, d), 7.03 (1H, d), 7.08 - 7.22 (3H, m), 7.28 - 7.41 (3H, m), 7.47 (2H, d). MS (APCI, neg.) 415.1 (M-1), 324.3.

5

EXAMPLE 27

(E)-3-(2-((E)-3-(2-HYDROXY-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-
2-PROPENOIC ACID

10 This product was obtained as a mixture with the other isomer
(E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-1-propenyl)phenyl)-2-propenoic
acid via a palladium coupling between 2-bromocinnamic acid and 2-alkyl-6-
methylphenol as in examples 6 and 7, step 2. The title acid was separated
from the other isomer by recrystallization from ether:hexane 1:1. Yield of
pure product: 48%.

15 ¹H NMR (Acetone-d₆) δ 2.20 (3H, s), 3.74 (2H, d), 6.34 ((1H, m),
6.44 (1H, d), 6.70 (1H, t), 6.80 (1H, d), 6.95 (1H, d), 7.22 (1H, d), 7.30 (1H, t),
7.35 (2H, m), 7.74 (1H, d), 8.10 (1H, d).

EXAMPLES 30 AND 31

20 (E)-3-(2-((E)-3-(2-((7-CHLORO-2-QUINOLINYLMETHOXY)-3-
METHYLPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-
3-(2-((E)-3-(2-((7-CHLORO-2-QUINOLINYLMETHOXY)-3-
METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

25 Step 1 Methyl (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-2-propenyl)phenyl)-
1-propenyl)phenyl)-2-propenoate and methyl (E)-3-(2-((E)-3-(2-hydroxy-3-
methylphenyl)-2-propenyl)phenyl)-2-propenyl)phenyl)-2-propenoate

30 These two products were prepared as a mixture via
esterification of the two acids in example 27 using the procedure of example
61, step 1.

Step 2

Treatment of the two esters of step 1 with 7-chloro-2-(bromomethyl)quinoline
(obtained by bromination of 7-chloroquinoline with N-bromosuccinimide) and
35 hydrolysis of the esters was performed as in example 61, steps 2 and 3.

MS (APCI, neg.) 470.0, 468.0 (M-1).

5

EXAMPLE 32

2-(3-(2-BENZYLOXY-3-METHYLPHENYL)PROPYL)BENZOIC ACID

3-Allyl-2-(benzyloxy)toluene (prepared as in examples 6 and 7, step 1) was treated with 9-BBN and then with ethyl 2-bromobenzoate as in example 20, step 1, to give the ester of the title compound. This ester was

10

hydrolyzed as in example 61, step 3.
¹H NMR (acetone d₆) δ 1.95 (2H, m), 2.30 (3H, s), 2.75 (2H, m), 3.08 (2H, dd), 4.70 (2H, s), 6.92 - 7.12 (3H, m), 7.24 - 7.53 (8H, m), 7.93 (1H, d).

15

EXAMPLES 33 AND 34

SODIUM 2-(3-(2-BENZYLOXY-3-METHYLPHENYL)-1-
PROPENYL)BENZOATE AND SODIUM 2-(3-(2-BENZYLOXY-3-
METHYLPHENYL)-2-PROPENYL)BENZOATE

20

3-allyl-2-(benzyloxy)toluene (prepared as in examples 6 and 7, step 1) was coupled to ethyl 2-bromobenzoate as in examples 6 and 7, step 2. The resulting ester was hydrolyzed as in example 61, step 3.

¹H NMR (acetone d₆) δ 2.25 and 2.32 (3H, 2s), 3.64 and 3.97 (2H, 2d), 4.76 and 4.93 (2H, 2s), 6.33 and 6.50 (1H, 2td), 6.68 - 7.64 (12H, m), 7.90 and 7.98 (1H, 2d).

25

The sodium salts were prepared as in examples 6 and 7, step 3.

EXAMPLE 35

SODIUM (E)-3-(2-(3-(2-BENZYLOXY-3-
METHYLPHENYL)PROPYL)PHENYL)-2-PROPENOATE

30

Step 1 2-(3-(2-benzyloxy-3-methylphenyl)propyl)benzaldehyde

3-allyl-2-(benzyloxy)toluene was treated with 9-BBN and then with 2-bromobenzaldehyde as in example 20, step 1, to give the title aldehyde. Yield 58%.

35

Step 2 Ethyl (E)-3-(2-(3-(2-benzyloxy-3-methylphenyl)propyl)phenyl)-2-propenoate

40

To the aldehyde of step 1 (850 mg, 2.47 mmol) was added (methoxycarbonylmethylene)triphenylphosphorane (1.24 g, 1.5 equiv.) and the mixture was heated to 80 C in 25 ml of toluene for 10 h.

- 5 NH_4Cl was added and the mixture was extracted in EtOAc, dried over Na_2SO_4 and the product was purified by flash chromatography with EtOAc:toluene 2.5:97.5. Yield: 770 mg, 78%.

Step 3

- 10 Hydrolysis of the ester was performed as in example 61, step 3.
MS (APCI, neg.) 385.1 (M-1).

The sodium salt was prepared as in examples 6 and 7, step 3.

The products of the following table were prepared in a manner similar to example 34.

15

Example #	MS (APCI, neg.)
36	401.2 (M-1), 310.0
37	401.2 (M-1), 310.0

EXAMPLE 42

SODIUM (E)-3-(2-((E)-3-(2-(BENZYLOXY)PHENYL)-3-HYDROXY-1-
PROPENYL)PHENYL)-2-PROPENOATE

20

Step 1 1-(2-(benzyloxy)phenyl)-2-propen-1-ol

- 2-(benzyloxy)benzaldehyde (5g, 23.6 mmol) was reacted with vinylmagnesium bromide in THF (90 ml) at 0 C. The reaction was quenched with 2 N HCl and the product was extracted in i-PrOAc, dried over Na_2SO_4
25 and purified by flash chromatography with EtOAc:toluene 2.5:97.5.

Step 2

- A mixture containing the allylic alcohol of step 1 (298 mg, 1.24 mmol), 2-bromocinnamic acid (299 mg, 1.06 equiv.), Bu_4NOAc (380 mg, 1 equiv.), Et_3N (1.2 ml), $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (26 mg, 0.03 equiv.) and DMF (5 ml) was degassed and heated to 100 C for 2 h. After addition of NH_4Cl and acidification with AcOH, the product was extracted in EtOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene:AcOH 10:90:5. Yield: 239 mg, 50%.

- 35 MS (APCI, neg.) 385.1 (M-1), 235.0

The sodium salt was prepared as in examples 6 and 7, step 3.

5

EXAMPLE 43

N2-((E)-3-(2-(3-(2-(BENZYLOXY)-3-METHYLPHENYL)PROPYL)PHENYL)-2-
PROPANOYL)-2-THIOPHENESULFONAMIDE, SODIUM SALT

The mixture of the two acylsulfonamides of examples 2 and 3 were reduced by catalytic hydrogenation using 10% Pd/C in EtOAc at atmospheric pressure for 3 days. Filtration through celite and purification by flash chromatography yielded the title sulfonamide.

¹H NMR (Acetone-d₆) δ 1.85 (2H, m), 2.30 (3H, s), 2.60 (4H, m), 2.71 (2H, t), 2.85 (2H, t), 4.70 (2H, s), 6.92 - 7.13 (7H, m), 7.20 (1H, dd), 7.30 - 7.50 (5H, m), 7.80 (1H, d), 7.95 (1H, d). MS (APCI, neg.) 531.9 (M-1).

The sodium salt was prepared as in examples 6 and 7, step 3.

EXAMPLES 44 AND 45

N2-((E)-3-(2-((E)-3-(4-(BENZYLOXY)-3-METHOXYPHENYL)-1-
PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE
AND N2-((E)-3-(2-((E)-3-(4-(BENZYLOXY)-3-METHOXYPHENYL)-2-
PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENE
SULFONAMIDE, SODIUM SALTS

The product of examples 14 and 15 (254 mg, 634 μmol) was dissolved in 6 ml CH₂Cl₂. DMF (10 μl) and oxalyl chloride (76 ml, 1.4 equiv.) were then added at 0 C and the solution was stirred at r.t. for 1.5 h. The solvent was evaporated and the resulting acid chloride was redissolved in CH₂Cl₂ (6 ml). At 0 C, 2-thiophenesulfonamide (124 mg, 1.2 equiv.) and Et₃N (177 μl, 2 equiv.) were added and the mixture was stirred at 0 C for 1 h. 0.5 N HCl was then added and the product was extracted in i-PrOAc, dried over Na₂SO₄ and purified by flash chromatography on silica using EtOAc:toluene:AcOH 20:80:1. Yield: 201 mg, 58%.

MS (APCI, neg.) 544.2 (M-1).

The sodium salts were prepared as in examples 6 and 7, step 3.

5

EXAMPLE 46 AND 47

SODIUM (E)-3-(2-((2-(2-(BENZYLOXY)-3-METHYLPHENYL)CYCLOPROPYL)METHYL)PHENYL)-2-PROPENOATE
AND SODIUM (E)-3-(2-(2-((2-(BENZYLOXY)-3-METHYLPHENYL)METHYL)CYCLOPROPYL)
10 PHENYL)-2-PROPENOATE

Step 1 Ethyl 2-((2-(2-(benzyloxy)-3-methylphenyl)cyclopropyl)methyl)benzoate and ethyl 2-(2-((2-(benzyloxy)-3-methylphenyl)methyl)cyclopropyl)benzoate

15

The intermediate ester of example 33 was treated with portions of CH_2N_2 solution in ether and $\text{Pd}(\text{OAc})_2$ alternatively and at 0 C until the reaction was complete. AcOH was added and the mixture was filtered through silica with ether and concentrated. This product was used as such in the next step.

20

Step 2 2-((2-(2-(benzyloxy)-3-methylphenyl)cyclopropyl)methyl)benzaldehyde and 2-(2-((2-(benzyloxy)-3-methylphenyl)methyl)cyclopropyl)benzaldehyde

25

To a solution of the ester of step 1 (3.68 mmol) in THF (20 ml) was added diisobutylaluminum hydride 1.0 M in toluene (16 ml, 4.4 equiv.) at -72 C and the mixture was stirred at -40 C for 10 min. The reaction was quenched with sodium potassium tartrate 1.0 M and was stirred at r.t. for 1.5 h. It was neutralized with AcOH and extracted in i-PrOAc. The product was dried over Na_2SO_4 and concentrated.

30

This benzylic alcohol was oxidized with activated MnO_2 (20 equiv.) in EtOAc at r.t. o.n. The mixture was then filtered through celite, concentrated and the aldehyde was purified by flash chromatography with toluene. Yield: 83% for steps 1 and 2.

35

Step 3

The aldehyde of step 2 was treated as in Example 34, steps 2 and 3, to afford the two title products. The sodium salts were prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 397.1 (M-1).

5

EXAMPLE 48

SODIUM (E)-3-(2-((E)-3-(2-BENZYLOXY-3-METHYLPHENYL)-3-HYDROXY-
1-PROPENYL)PHENYL)-2-PROPENOATE

- 10 Step 1 Methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-3-acetoxy-1-propenyl)phenyl)-2-propenoate and methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-1-acetoxy-2-propenyl)phenyl)-2-propenoate.

15 The two products of examples 28 and 29 were esterified with NaH and MeI as in example 61, step 1. These esters (928 mg, 2.33 mmol) were heated to reflux in AcOH (15 ml) with SeO₂ (310 mg, 1.2 equiv.) for 15 min. After neutralization with NaHCO₃, the products were extracted in EtOAc, dried over Na₂SO₄ and purified by flash chromatography with EtOAc:toluene 5:95.

- 20 Step 2 Methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-3-hydroxy-1-propenyl)phenyl)-2-propenoate

The product of step 1 (2.3 mmol) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (3 drops) in MeOH (10 ml) for 2 h. After evaporation, the title product was separated from the less polar cyclized isomer (methyl 2-(3-((E)-2-(2-(benzyloxy)-3-methylphenyl)-1-ethenyl)-1,3-dihydro-1-isobenzofuranyl)acetate) by flash chromatography with EtOAc:toluene 2.5:97.5 and 5:95.

Step 3

- 30 Hydrolysis was performed as in example 61, step 3. The sodium salt was prepared as in examples 6 and 7, step 3.
MS (APCI, neg.) 399.1 (M-1), 249.0.

5

EXAMPLES 50 AND 51

(E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-3-HYDROXY-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-1-HYDROXY-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

10

Step 1 (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzoyloxy)-3-methylphenyl)-3-acetoxy-1-propenyl)phenyl)-2-propenoic acid and (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzoyloxy)-3-methylphenyl)-1-acetoxy-2-propenyl)phenyl)-2-propenoic acid

15

The product of example 61 was treated with SeO₂ in AcOH as in example 48, step 1 to afford the two title acetates. Yield: 92%.

Step 2

20

The two acetates of step 1 (153 mg, 282 μ mol) were heated in AcOH:H₂O 1:1 (14 ml) at 105 C for 45 min. After addition of NH₄Cl, the products were extracted in EtOAc, dried over Na₂SO₄ and purified by flash chromatography with EtOAc:toluene:AcOH 10:90:1. The two products were separated by HPLC on a NovaPak C18 cartridge using MeOH:(1:1 AcOH:AcONa 2 g/L) 7:3 and UV detection at 280 nm.

25

The more polar product was (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzoyloxy)-3-methylphenyl)-1-hydroxy-2-propenyl)phenyl)-2-propenoic acid. Yield: 28 mg.

¹H NMR (acetone d₆) δ 2.10 (3H, s), 5.20 (2H, s), 5.73 (1H, d), 6.20 (1H, d), 6.47 (1H, dd), 6.97 (1H, t), 7.04 (1H, d), 7.10 (1H, d), 7.37 - 7.48 (6H, m), 7.63 (1H, d), 7.72 (1H, d), 8.35 (1H, d). MS (APCI, neg.)

30

decomposition.

The less polar isomer was (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzoyloxy)-3-methylphenyl)-3-hydroxy-1-propenyl)phenyl)-2-propenoic acid.

Yield: 17 mg.

MS (APCI, neg.) 467.0 (M-1), 291.0.

35

5

EXAMPLE 58 AND 59

(E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-(HYDROXYMETHYL)PHENYL)-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-(HYDROXYMETHYL)PHENYL)-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

10

Step 1 3-allyl-2-(2,6-dichlorobenzoyloxy)benzaldehyde

2-(allyloxy)benzaldehyde (2.00 g, 12.33 mmol) was heated in o-dichlorobenzene (20 ml) at reflux o.n. The mixture was poured on top of a flash chromatography column and eluted with toluene:hexane 1:1.

15

Yield: 1.346 g, 67%.

Step 2

The phenol of step 1 was treated with NaH and 2,6-dichlorobenzyl bromide as in examples 6 and 7, step 1, to give the benzyl ether. Then, the aldehyde was reduced with diisobutylaluminum hydride in THF at -10 C for 15 min. (see examples 46 and 47, step 2). Finally, a palladium coupling with 2-bromocinnamic acid was performed as in examples 6 and 7, step 2, to give the two title isomers.

20

25

Overall yield: 65%.

MS(APCI, neg.) 467.1 (M-1), 291.1.

EXAMPLE 61

SODIUM (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

30

Step 1 Methyl (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-2-propenyl)phenyl)-2-propenoate

The product of example 27 (2.001 g, 6.80 mmol) was dissolved in DMF (14 ml) and NaH 80% in oil (244 mg, 1.2 equiv.) was added at 0 C. The mixture was stirred for an hour at 0 C, then MeI (635 μ l, 1.5 equiv.) was added and the stirring continued for 2 h. After hydrolysis with 0.5 N HCl, the product was extracted in EtOAc and purified by flash chromatography on silica with EtOAc:toluene 2.5:97.5 and 5:95. Yield: 1.70 g, 81%.

35

5

Step 2 Methyl (E)-3-(2-(((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-2-propenyl)phenyl)-2-propenoate

The product of step 1 was treated with NaH and 2,6-dichlorobenzyl bromide as in examples 6 and 7, step 1, to afford the dichlorobenzyl ether.

Step 3

The ester (1.01 g, 2.18 mmol) was hydrolyzed with NaOH 10 N (930 μ l) in THF:MeOH:H₂O 4:2:1 (28 ml) at r.t. o.n.. The reaction was quenched with sat. NH₄Cl, acidified with acetic acid and the product was extracted in EtOAc, concentrated and recrystallized in 20 ml ether:hexane 1:1. Yield: 746 mg, 75%.

The sodium salt was prepared as in examples 6 and 7, step 3.
MS (APCI, neg.) 452.0, 451.0 (M-1), 275.2.

The following compounds were prepared as in example 61.

Example #	MS(APCI, neg.) ^a
28	383.2
53	401.1, 275.2
55	419.1, 275.2
57	419.1, 275.2
63	451.1, 275.2
65	449.1, 275.2

a) M-1.

EXAMPLE 70

SODIUM (E)-3-(2-(3-PHENOXYBENZYLOXYMETHYL)PHENYL)-2-PROPENOATE

Step 1 Ethyl (E)-3-[2-(bromomethyl)phenyl]-2-propenoate

To a suspension of ethyl (E)-3-(2-methylphenyl)-2-propenoate (20.0 g; 105 mmol) and NBS (19.64 g; 110.3 mmol) in refluxing CCl₄ was added benzoyl peroxide (1.27 g) and the mixture was stirred for 12 h. The

- 5 solution was cooled to r.t., filtered and concentrated. Flash chromatography with EtOAc:hexane 5:95 yielded the title compound (14.18 g, 50%).

^1H NMR (CDCl_3) δ 1.30 (3H, t), 4.25 (2H, q), 4.60 (2H, s), 6.45 (1H, d), 7.30 (3H, m), 7.57 (1H, m) and 8.05 (1H, d).

10 Step 2 Ethyl (E)-3-(2-((3-phenoxy)benzyloxy)phenyl)-2-propenoate

To a solution of 3-phenoxybenzylalcohol (545 mg; 2.72 mmol) in DMF (5 ml) was added NaH (92 mg; 3.1 mmol; 80% dispersion in oil) and ethyl (E)-3-(2-(bromomethyl)phenyl)-2-propenoate (810 mg; 3.0 mmol). After 6 h at r.t., 20 mg extra NaH was added. The final mixture was stirred at r.t. for 10 h then quenched using 0.3 ml of AcOH. The mixture was diluted with Et_2O (25 ml), washed with water (3 x 20 ml) and brine, dried over MgSO_4 and concentrated. Flash chromatography with EtOAc:toluene 5:95 afforded the desired material.

Yield: 822 mg, 78%.

20 Step 3

The ester of step 2 was hydrolyzed as in example 61, step 3, to yield the title acid. The sodium salt was prepared as in examples 6 and 7, step 3.

25 MS (APCI, neg.) 359.0 (M-1).

EXAMPLE 71

SODIUM (E)-3-(2-(2-PHENOXYBENZYLOXYMETHYL)PHENYL)
-2-PROPENOATE

30 This product was prepared as in example 70 from 2-phenoxybenzyl alcohol.

MS (APCI, neg.) 359.0 (M-1).

5

EXAMPLE 74

SODIUM (E)-3-(2-(3-(2-BENZYLOXYPHENOXY)PROPOXY)PHENYL)-2-
PROPENOATEStep 1 Methyl (E)-3-(2-(3-bromopropoxy)phenyl)-2-propenoate

10

To a solution of methyl 2-hydroxycinnamate (1.31 g; 7.33 mmol) in 50 ml acetone was added 1,3-dibromopropane (1.50 ml; 14.8 mmol) and K₂CO₃ (4.36 g; 13.4 mmol). The mixture was heated to reflux for 12h, cooled to r.t, diluted with hexane (50 ml), filtered and finally concentrated to afford the title product (1.96 g; 50% pure), which was used as such in the next step.

15

Step 2

2-Benzyloxyphenol (obtained from catechol, NaH, and benzyl bromide as in examples 6 and 7, step 1) was treated with NaH and the product of step 1 as in examples 6 and 7, step 1 to afford the ester of the title product. This ester was hydrolyzed as in example 61, step 3 to yield the acid. The sodium salt was prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 403.1 (M-1), 233.1, 207.1.

EXAMPLE 75

25

SODIUM (E)-3-(2-((E)-3-(2-(1-PHENYLETHOXY)-3-METHYLPHENYL)-2-
PROPENYL)PHENYL)-2-PROPENOATE

30

1-Phenylethanol was obtained by reduction of acetophenone with NaBH₄ in THF:MeOH. It was then reacted with the ester of example 61, step 1, via a Mitsunobu reaction (DIAD, Ph₃P, THF:CH₂Cl₂, Synth. Commun. 1994, 24, 1049), to yield the ester of the title compound. This ester was hydrolyzed as in example 61, step 3, to give the title acid.

The sodium salt was prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 397.1 (M-1), 293.0, 275.3, 233.2.

5

EXAMPLES 77 AND 78

SODIUM (E)-3-(2-((E)-3-(3-PHENOXYPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOATE AND SODIUM (E)-3-(2-((E)-3-(3-PHENOXYPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

10

Step 1 1-bromo-3-phenoxybenzene

To a solution of phenol (5.08g; 54mmol) in 30 ml dry DMF at 0°C was added portionwise NaH (1.98 g; 66 mmol; 80% dispersion in oil). The mixture was stirred 30 min at r.t. then 1,3-dibromobenzene (33 ml; 273 mmol) and Cu₂O (3.95 g; 28 mmol) were added. The final mixture was heated to reflux for 4h, cooled to r.t., diluted with Et₂O (200 ml), washed with water (3 x 200 ml), NaOH (1.0 M; 2 x 100 ml) and brine, dried over MgSO₄ and concentrated. Flash chromatography with hexane afforded the desired material.

15

Yield: 7.62 g, 57%.

20

Step 2 1-allyl-3-phenoxybenzene

A suspension of 1-bromo-3-phenoxybenzene (2.01 g; 8.08 mmol), PdCl₂(PPh₃)₂ (296 mg ; 0.42 mmol), allyl tributyltin (3.13 g ; 9.46 mmol), triphenylphosphine (455 mg; 1.73 mmol) and LiCl (1.39 g; 33 mmol) in 10 ml DMF was stirred at 100°C for 3h. After cooling to r.t the mixture was diluted with Et₂O (75 ml), washed with water (3 x 50 ml) and brine, dried over MgSO₄ and concentrated. Flash chromatography with hexane afforded the desired material.

25

Yield: 1.39g, 81%.

30

Step 3

Using the procedure of examples 6 and 7, steps 2 and 3, the product of step 2 was transformed to the title compounds.

MS (APCI, neg.) 355.1 (M-1), 311.2.

35

5

EXAMPLES 79 AND 80

SODIUM (E)-3-(2-((E)-3-(3-PHENYLBENZO[*b*]FURAN-7-YL)-1-PROPENYL)PHENYL)-2-PROPENOATE AND SODIUM (E)-3-(2-((E)-3-(3-PHENYLBENZO[*b*]FURAN-7-YL)-2-PROPENYL)PHENYL)-2-PROPENOATE

10

Step 1 2-(2-bromophenoxy)-1-phenyl-1-ethanone

To a solution of 2-bromophenol (8.71 g; 50.3 mmol) and bromoacetophenone (10.1 g; 50.5 mmol) in 50 ml acetone was added K₂CO₃ (7.02 g; 50.8 mmol). The mixture was heated to reflux for 10 h, cooled to r.t., filtered, diluted with EtOAc (100 ml), washed with HCl (1.0 M, 2 x 100 ml) and brine, dried over MgSO₄ and concentrated. The residual solid was recrystallized from EtOAc:hexane to afford the desired material.

15

Yield: 11.6 g, 79%.

20

Step 2 3-phenylbenzo[*b*]furan-7-yl-bromide

A mixture of 2-(2-bromophenoxy)-1-phenyl-1-ethanone (6.31 g) and polyphosphoric acid (285 g) was stirred at 95°C for 6 h. The resulting solution was cooled to 50°C, poured in water (2 L), extracted with Et₂O (2 x 1 L). The combined organic extracts were washed with water (4 x 500 ml) and brine, dried over MgSO₄ and concentrated. The residual solid was filtered on a plug of silica gel using Et₂O. Recrystallization in hot hexane yielded the title compound (4.63g; 78%).

25

Step 3

30

Using the procedure of examples 77 and 78, steps 2 and 3, the bromide of step 2 was transformed to the title acid. The sodium salts were prepared as in examples 6 and 7, step 3.
MS (APCI, neg.) 379.4 (M-1), 335.1.

5 WHAT IS CLAIMED IS:

1. A compound represented by formula II:



II

10 or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar¹ is an aryl or heteroaryl group, optionally substituted with R¹ or R³;

R¹ is Y_m-R², Y_m-Ar³, halogen, N(R⁵)₂, CN, NO₂, C(R⁶)₃, CON(R⁵)₂, S(O)_nR⁷ or OH;

15 Y represents a linker between R² or Ar³ and Ar¹ containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker optionally containing CO, S(O)_n, -C=C- or an acetylenic group, and said linker being optionally substituted by R²;

m is 0 or 1;

20 n is 0, 1 or 2;

R² represents H, F, CHF₂, CF₃, lower alkyl or hydroxyC₁₋₆ alkyl, or two R² groups may be joined together and represent a carbocyclic ring of up to six members, said ring containing not more than one heteroatom selected from O, N and S;

25 Ar³ represents an aryl or heteroaryl group, optionally substituted with R³;

R³ is R⁴, halogen, haloC₁₋₆alkyl, N(R⁵)₂, CN, NO₂, C(R⁶)₃, CON(R⁵)₂, OR⁴, SR⁴ or S(O)_nR⁷;

R⁴ is H, lower alkyl, lower alkenyl, lower alkynyl, CHF₂ or CF₃;

30 R⁵ is R⁴, Ph or Bn, or two R⁵ groups in combination with the atom to which they are attached represent a ring of up to 6 members containing carbon atoms and up to 2 heteroatoms selected from O, N and S;

R⁶ is H, F, CF₃ or lower alkyl, or two R⁶ groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;

35 R⁷ is lower alkyl, lower alkenyl, lower alkynyl, CHF₂, CF₃, N(R⁵)₂, Ph(R⁸)₂ or CH₂Ph(R⁸)₂;

R⁸ is R⁴, OR⁴, SR⁴ or halogen

5 W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, S(O)_n, C=C or an acetylenic group, and optionally being substituted with R⁹;

R⁹ is R², lower alkenyl, lower alkynyl, OR⁴ or SR⁴;

10 Ar² represents an aryl or heteroaryl group, optionally substituted with R³;

R¹⁰ represents R⁴, halogen, N(R⁵)₂, CN, NO₂, C(R⁶)₃, OR⁴, SR⁴ or S(O)_nR⁷;

15 X represents a linker which is attached to Ar² ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, S(O)_n, C=C or an acetylenic group, and said linker being optionally substituted with R¹¹;

R¹¹ is R⁹;

20 Q represents a member selected from the group consisting of: CO₂H, tetrazole, SO₃H, hydroxamic acid, CONHSO₂R¹² and SO₂NHCOR¹²;

R¹² represents a member selected from the group consisting of: CF₃, lower alkyl, lower alkenyl, lower alkynyl and ZAr⁴, wherein Z is an optional linker containing 0-4 carbon atoms, optionally substituted with R¹³;

25 R¹³ is R⁹;

Ar⁴ is an aryl or heteroaryl group optionally substituted with R¹⁴, and

R¹⁴ is R¹⁰ or NHCOMe.

30 2. A compound in accordance with claim 1 wherein R¹ is OH, OCH₂Ar³, SCH₂Ar³, OAr³, SAr³ or NR²CH₂Ar³.

35 3. A compound in accordance with claim 1 wherein Ar³ is an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R³.

4. A compound in accordance with claim 1 wherein Ar² is an aryl or heteroaryl group selected from the group consisting of: benzene,

5 pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with 1-5 groups selected from R⁴, OR⁴, SR⁴ and halogen.

5. A compound in accordance with claim 1 wherein W is selected from the group consisting of: CH₂OCH₂, (CH₂)₃, CH₂CH=CH,
10 CH=CHCH₂, CH(OH)CH=CH, CH=CHCH(OH), CH₂C+C, C+CCH₂, 1,2-c-Pr-CH₂ and -1,2-c-Pr-CH₂-.

6. A compound in accordance with claim wherein X is selected from the group consisting of: (CH₂)₂, CH=CH, C+C and 1,2-c-Pr.
15

7. A compound in accordance with claim 1 wherein Q is CO₂H or tetrazole.

8. A compound in accordance with claim 1 wherein Z represents a 0-2 carbon atom linker that is unsubstituted.
20

9. A compound in accordance with claim 1 wherein Ar⁴ represents an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and
25 naphthalene, said group being optionally substituted with R³.

10. A compound in accordance with claim 1 wherein:
Ar¹ is an aryl or heteroaryl group substituted by R¹ and R³;
R¹ is OH, OCH₂Ar³, SCH₂Ar³, OAr³, SAr³ or NR²CH₂Ar³;
30 Ar³ is selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R³;

Ar² represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, and thiazole, said group being
35 optionally substituted with 1-4 members selected from the group consisting of: R⁴, OR⁴, SR⁴ and halogen;

W is selected from the group consisting of: CH₂OCH₂, (CH₂)₃, CH₂CH=CH, CH=CHCH₂, CH(OH)CH=CH, CH=CHCH(OH), CH₂C+C, C+CCH₂, 1,2-c-Pr-CH₂- and -CH₂-1,2-c-Pr-;

5 X is selected from the group consisting of: $(CH_2)_2$, $CH=CH$,
C+C and 1,2-c-Pr;
and Q is CO_2H or tetrazole.

10 11. A compound in accordance with claim 1 wherein:
 Ar^1 is an aryl or heteroaryl group optionally substituted with R^1
and R^3 ;

R^1 is OH, OCH_2Ar^3 , SCH_2Ar^3 , OAr^3 , SAr^3 or $NR_2CH_2Ar^3$;

Ar^3 represents a member selected from the group consisting of:
benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being
15 optionally substituted with R^3 ;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$,
 $CH_2CH=CH$, $CH=CHCH_2$, $CH(OH)CH=CH$, $CH=CHCH(OH)$, CH_2C+C or
 $C+CCH_2$;

20 Ar^2 represents a member selected from the group consisting of:
benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being
optionally substituted with R^8 ;

X is selected from the group consisting of: $(CH_2)_2$, $CH=CH$,
C+C and 1,2-c-Pr;

Q is $CONHSO_2ZAr^4$;

25 Z is a 0-2 carbon linker and is unsubstituted;

Ar^4 is selected from the group consisting of: benzene, pyridine,
thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, and is
optionally substituted by R^3 .

30 12. A compound in accordance with claim 1 wherein:
 Ar^1 is benzene or thiophene substituted in position 2 and/or
position 4 relative to the attachment of W with a member selected from the
group consisting of: OH, OCH_2Ar^3 , SCH_2Ar^3 , OAr^3 , SAr^3 and $NR^2CH_2Ar^3$,
and is optionally substituted in position 3 with a member selected from the
35 group consisting of: OMe, $OCHF_2$ and lower alkyl;

Ar^3 is benzene or thiophene, optionally substituted with R^8 ;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$,
 $CH_2CH=CH$, $CH=CHCH_2$, $CH(OH)CH=CH$ and $CH=CHCH(OH)$,

5 Ar^2 is benzene or thiophene, optionally substituted with 1-4 members selected from R^4 , OR^4 , SR^4 and halogen;

X represents a member selected from the group consisting of: $(\text{CH}_2)_2$, $\text{CH}=\text{CH}$ and 1,2-c-Pr, and

Q is CO_2H .

10

13. A compound in accordance with claim 1 wherein:

Ar^1 is a benzene or a thiophene unsubstituted or substituted in position 2 and/or position 4 relative to the point of attachment to W by a member selected from the group consisting of: OH , OCH_2Ar^3 , SCH_2Ar^3 , OAr^3 , SAr^3 and $\text{NR}^2\text{CH}_2\text{Ar}^3$; and is optionally substituted at position 3 with one member selected from the group consisting of: OMe , OCHF_2 and lower alkyl;

15

Ar^3 is benzene or thiophene, optionally substituted with R^8 ;

20 W is selected from the group consisting of: CH_2OCH_2 , $(\text{CH}_2)_3$, $\text{CH}_2\text{CH}=\text{CH}$, $\text{CH}=\text{CHCH}_2$, $\text{CH}(\text{OH})\text{CH}=\text{CH}$ and $\text{CH}=\text{CHCH}(\text{OH})$;

Ar^2 is benzene or thiophene, optionally substituted with R^4 , OR^4 , SR^4 or halo;

X is selected from the group consisting of: $(\text{CH}_2)_2$, $\text{CH}=\text{CH}$ and 1,2-c-Pr,

25

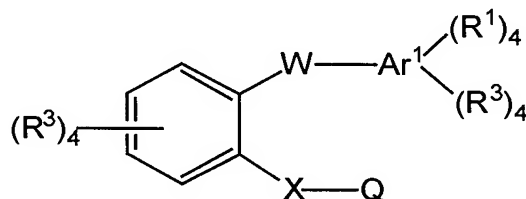
Q is $\text{CONHSO}_2\text{ZAr}^4$,

Z is a bond or CH_2 , and

Ar^4 is selected from the group consisting of: benzene, thiophene, 1,3,4-thiadiazole and naphthalene and is substituted with R^8 .

30

14. A compound represented by formula II':



II'

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar¹ represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R¹ represents H, OH, C₁-6alkyl, C₁-6alkoxy, hydroxyC₁-6alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R³ represents R⁴, halogen, OR⁴ or SR⁴;

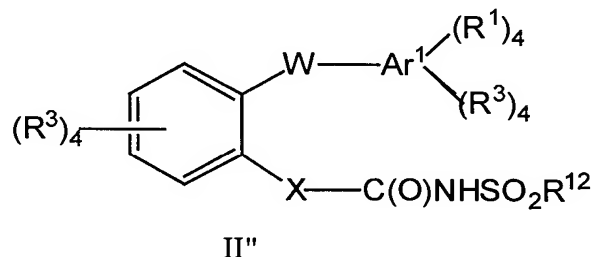
R⁴ represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF₂ or CF₃;

X represents a member selected from the group consisting of: -(CH₂)₁₋₂-, 1,2-c-Pr-, -CH=CH-, -CH₂O-, -C⁺CCH₂-, -C⁺C-, and -CH₂-C⁺C-;

W represents a member selected from the group consisting of: -(CH₂)₃₋₆-, -CH₂CH=CH-, -CH=CHCH₂-, -CH(OH)CH=CH-, -CH=CHCH(OH)-, -CH₂-1,2-c-Pr-, -1,2-c-Pr-CH₂-, , -CH₂-O-CH₂-, -O-(CH₂)₁₋₃-O-, -CH₂-NHC(O)-, -CF₂CH=CH-, -CH=CHCF₂-, -CH₂CH₂-S-, -S-CH₂CH₂-, -CH₂CH₂-SO₂-, -SO₂-CH₂CH₂-, -O-(CH₂)₁₋₃-, -(CH₂)₁₋₃-O- and -CH=CHCH₂CH₂-, and

all other variables are as defined in claim 1.

15. A compound represented by formula II'':



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar¹ represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R¹ represents H, OH, C₁-6alkyl, C₁-6alkoxy, hydroxyC₁-6alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R³ represents R⁴, halogen, OR⁴ or SR⁴;

- 5 R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;

X represents a member selected from the group consisting of:

- 10 $-(CH_2)_{1-2}$ -, $-1,2-c-Pr$ -, $-CH=CH$ -, $-CH_2O$ -, $-C^+CCH_2$ -, $-C^+C$ -, and $-CH_2-C^+C$ -;

W represents a member selected from the group consisting of:

- 15 $-(CH_2)_{3-6}$ -, $-CH_2CH=CH$ -, $-CH=CHCH_2$ -, $-CH(OH)CH=CH$ -, $-CH=CHCH(OH)$ -, $-CH_2-1,2-c-Pr$ -, $-1,2-c-Pr-CH_2$ -, $-CH_2-O-CH_2$ -, $-O-(CH_2)_{1-3}-O$ -, $-CH_2-NHC(O)$ -, $-CF_2CH=CH$ -, $-CH=CHCF_2$ -, $-CH_2CH_2-S$ -, $-S-CH_2CH_2$ -, $-CH_2CH_2-SO_2$ -, $-SO_2-CH_2CH_2$ -, $-O-(CH_2)_{1-3}$ -, $-(CH_2)_{1-3}-O$ - and $-CH=CHCH_2CH_2$ -, and

- 20 R^{12} is selected from the group consisting of: C_{1-6} alkyl, thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl, $-CH=CH$ -phenyl, said thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl and $-CH=CH$ -phenyl groups being optionally substituted with R^3 .

- 25 16. A compound in accordance with claim 1 falling within the following table:

Table I					
(Ar ¹ -W-Ar ² -X-Q)					
Ex	Ar ¹	W	Ar ²	X	Q
1	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	$(CH_2)_2$	CO ₂ H
2	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
3	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
4	2-((2-Cl-4-FPh)CH ₂ O)-3-CF ₃ Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO ₂ H
5	2-((2-Cl-4-FPh)CH ₂ O)-3-CF ₃ Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO ₂ H
6	2-(BnO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺

7	2-(BnO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
8	4-(BnO)-3,5-(MeO) ₂ Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
9	4-(BnO)-3,5-(MeO) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
10	2-(BnO)-5-AcPh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
11	2-(BnO)-5-AcPh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
12	2-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
13	2-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
14	4-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
15	4-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
16	2-(BnO O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH ₂	CO ₂ ⁻ X ⁺
17	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH ₂	CO ₂ ⁻ X ⁺
18	2-(BnO)-3-MePh	CH ₂ CH=CH	5-Cl-1,2-Phe	CH ₂	CO ₂ ⁻ X ⁺
19	2-(BnO)-3-MePh	CH=CHCH ₂	5-Cl-1,2-Phe	CH ₂	CO ₂ ⁻ X ⁺
20	4-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	1,2-c-Pr	CO ₂ H
21	2-(BnO)-3-MePh	CH=CHCH ₂	4,5-(MeO) ₂ -1,2-Phe	CH=CH	CO ₂ H
22	2-(BnO)-3-MePh	CH ₂ CH=CH	4,5-(MeO) ₂ -1,2-Phe	CH=CH	CO ₂ H
23	3,4-(methylene dioxo)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
24	3,4-(methylene dioxo)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
25	Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
26	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
27	2-(HO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
28	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
29	2-(BnO)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
30	2-((7-Cl-2-quinoliny)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
31	2-((7-Cl-2-quinoliny)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
32	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	bond	CO ₂ H
33	2-(BnO)-3-MePh	CH=CHCH ₂	1,2-Phe	bond	CO ₂ ⁻ X ⁺
34	2-(BnO)-3-MePh	CH ₂ CH=CH	1,2-Phe	bond	CO ₂ ⁻ X ⁺
35	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
36	2-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺

37	4-(BnO)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
38	4-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
39	4-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
40	3,4-(MeO) ₂ Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
41	3,4-(MeO) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
42	2-(BnO)Ph	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
43	2-(BnO)-3-MePh	(CH ₂) ₃	1,2-Phe	(CH ₂) ₂	CON ⁻ X ⁺ SO ₂ - 2-thienyl
44	4-(BnO)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CON ⁻ X ⁺ SO ₂ - 2-thienyl
45	4-(BnO)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CON ⁻ X ⁺ SO ₂ - 2-thienyl
46	2-(BnO)-3-MePh	CH ₂ -1,2-c-Pr	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
47	2-(BnO)-3-MePh	1,2-c-Pr-CH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
48	2-(BnO)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
49	2-(BnO)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
50	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
51	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO ₂ H
52	2-((4-FPh)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
53	2-((4-FPh)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
54	2-((3,4-F ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
55	2-((3,4-F ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
56	2-((3,5-F ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
57	2-((3,5-F ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
58	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
59	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H

60	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
61	2-((2,6-Cl ₂ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
62	2-((4-CF ₃ Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
63	2-((4-CF ₃ Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
64	2-((4-(CHF ₂ O)Ph)CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
65	2-((4-(CHF ₂ O)Ph)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
66	2-((4-CF ₃ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
67	2-((4-CF ₃ Ph)CH ₂ O)-3-(HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
68	2-((4-CF ₃ Ph)CH ₂ O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO ₂ H
69	2-(PhCH ₂ O)-3-(HOCH ₂)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
70	3-(PhO)Ph	CH ₂ OCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
71	2-(PhO)Ph	CH ₂ OCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
72	3-(BnO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
73	3-(BnO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
74	2-(BnO)Ph	O(CH ₂) ₃ O	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
75	2-(PhCHMeO)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
76	2-(PhCHMeO)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
77	3-(PhO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
78	3-(PhO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
79	3-Phbenzo furan-7-yl	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
80	3-Phbenzo furan-7-yl	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ ⁻ X ⁺
81	Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
82	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
83	4-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl
84	4-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -2-thienyl

85	2-(BnO)-1-naphthyl	CH ₂ NHCO	1,2-Phe	CH=CH	CO ₂ H
86	2-((2-Cl-4-FPh) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
87	2-((2-Cl-4-FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
88	2-((2,4- F ₂ Ph)CH ₂ O) -3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
89	2-((2,4-F ₂ Ph) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
90	2-((2,4,6-F ₃ Ph) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
91	2-((2,4,6-F ₃ Ph) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
92	2-((2,6-Cl ₂ -4-FPh) CH ₂ O)-3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
93	2-((2,6-Cl ₂ -4-FPh) CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
94	2-((2,4- F ₂ Ph)CH ₂ O) -3-(CHF ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
95	2-((2,4- F ₂ Ph)CH ₂ O) -3-(CHF ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
96	2-((4-FPh)CH ₂ O) -3-MePh	CF ₂ CH=CH	1,2-Phe	CH=CH	CO ₂ H
97	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCF ₂	1,2-Phe	CH=CH	CO ₂ H
98	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ - (4-i-PrPh)
99	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ - (4-t-BuPh)
100	2-((4-FPh)CH ₂ O) -3-MePh	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ - (4-(MeO)Ph)
101	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2,3- Cl ₂ Ph)
102	2-((4-FPh)CH ₂ O) -3-MePh	CH=CHCH ₂	4-Cl-1,2- Phe	CH=CH	CONHSO ₂ -(5- Br-2-(MeO)Ph)
103	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₂ S	3-F-1,2-Phe	CH=CH	CONHSO ₂ - (2,3,4-Cl ₃ Ph)
104	2-((4-FPh)CH ₂ O)-3- MePh	(CH ₂) ₂ S	6-CF ₃ -1,2- Phe	CH=CH	CONHSO ₂ -(5-F- 2-MePh)
105	2-((4-FPh)CH ₂ O)-3- MePh	(CH ₂) ₂ S	4,5-F ₂ -1,2- Ph	CH=CH	CONHSO ₂ - (2,5-Me ₂ Ph)
106	2-((4-FPh)CH ₂ O)-3- MePh	(CH ₂) ₂ SO ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4- CF ₃ Ph)
107	2-((4-FPh)CH ₂ O)-3- MePh	(CH ₂) ₂ SO ₂	1,2-Phe	CH=CH	CONHSO ₂ -2- naphthyl

108	2-((4-FPh)CH ₂ O)-3-MePh	CH=CHCH ₂	3-F-1,2-Phe	CH=CH	CONHSO ₂ -(3-Cl-4-FPh)
109	2-((4-FPh)CH ₂ O)-3-MePh	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4-n-PrPh)
110	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2-ClPh)
111	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	SO ₂ (CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4-FPh)
112	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	S(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2-PhPh)
113	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	S(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2-CF ₃ Ph)
114	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	S(CH ₂) ₂	4-t-Bu-1,2-Phe	CH=CH	CONHSO ₂ -(4-Cl-2,5-Me ₂ Ph)
115	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2,5-Cl ₂ Ph)
116	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -(4-Br-2-(CF ₃ O)Ph)
117	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	O(CH ₂) ₂	1,2-Phe	CH=CH	CONHSO ₂ -CH ₂ Ph
118	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	(CH ₂) ₂ O	1,2-Phe	CH=CH	CONHSO ₂ -1-naphthyl
119	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	(CH ₂) ₂ O	4,5-F ₂ -1,2-Phe	CH=CH	CONHSO ₂ -(2-FPh)
120	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	(CH ₂) ₂ O	1,2-Phe	CH=CH	CONHSO ₂ -(2,4-Cl ₂ Ph)
121	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -CH=CHPh
122	2-((4-FPh)CH ₂ O)-3-(MeO)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -(3,5-(CF ₃) ₂ Ph)
123	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₃	1,2-Phe	CH=CH	CONHSO ₂ -(2,5-Cl ₂ -3-thienyl)
124	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₄	3-F-1,2-Phe	CH=CH	CONHSO ₂ -(3-BrPh)
125	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₄	3-MeO-1,2-Phe	CH=CH	CONHSO ₂ -(2-BrPh)
126	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₄	1,2-Phe	CH=CH	CONHSO ₂ -(2-NO ₂ Ph)
127	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₅	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(3-ClPh)
128	2-((4-FPh)CH ₂ O)Ph	(CH ₂) ₅	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4-(CF ₃ O)Ph)
129	2-HOPh	CH=CH(CH ₂) ₂	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -8-quinoliny
130	2-((4-FPh)CH ₂ O)Ph	CH=CH(CH ₂) ₂	5-(CF ₃ O)-1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(3,4-Cl ₂ Ph)

131	4-((2,6-Cl ₂ -4-FPh)CH ₂ O)-3-MePh	CH=CH(CH ₂) ₂	3-F-1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4-EtPh)
132	2-((4-FPh)CH ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	(CH ₂) ₂	CONHSO ₂ -(4-Cl-2-NO ₂ Ph)
133	2-((4-FPh)CH ₂ O)Ph	CH=CHCH ₂	4,5-F ₂ -1,2-Phe	CH=CH	CONHSO ₂ -(2-Cl-3-Br-5-thienyl)
134	2-((4-FPh)CH ₂ O)Ph	CH ₂ CH=CH	4,5-F ₂ -1,2-Phe	CH=CH	CONHSO ₂ -(3,4-(MeO) ₂ Ph)
135	2-HOPh	CH=CHCH ₂	4,5-F ₂ -1,2-Phe	CH=CH	CONHSO ₂ -(2,5-Cl ₂ -3-Br-4-thienyl)
136	4-((4-FPh)CH ₂ O)-3-(MeO)Ph	CH ₂ CH=CH	4,5-F ₂ -1,2-Phe	CH=CH	CONHSO ₂ -(4-Br-2,5-F ₂ Ph)
137	4-((4-FPh)CH ₂ O)-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(5-(AcNH)-1,3,4-thiadiazol-2-yl)
138	4-((4-FPh)CH ₂ O)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -(2,3,4,5,6-F ₅ Ph)
139	4-((2-Cl-4-FPh)CH ₂ O)-3-MePh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2-CNPh)
140	2-((4-FPh)CH ₂ O)Ph	CH ₂ CH=CH	4-F-1,2-Phe	CH=CH	CONHSO ₂ -(2-Cl-6-MePh)
141	2-HOPh	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ -(2,4,6-Me ₃ Ph)
142	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -(2,3-Br ₂ -2-thienyl)
143	2-((4-FPh)CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH ₂ O	CONHSO ₂ -(4-NO ₂ Ph)
144	2-((4-FPh)CH ₂ O)Ph	CH ₂ CH=CH	1,2-Phe	CH ₂ O	CONHSO ₂ -(3,5-Cl ₂ Ph)
145	2,4-((4-FPh)CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	prop-1-yne-1,3-diyl	CONHSO ₂ -(5-Cl-2-thienyl)
146	4-((2,4-F ₂ Ph)CH ₂ O)-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	CH ₂ O	CONHSO ₂ -(4-CF ₃ Ph)
147	2-HO-3-MePh	CH=CHCH ₂	1,2-Phe	CH ₂ O	CONHSO ₂ -(2,4-F ₂ Ph)
148	2-((4-FPh)CH ₂ O)Ph	CH ₂ CH=CH	4-F-1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -(4-ClPh)
149	2-((4-FPh)CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -(3-CF ₃ Ph)
150	4-HOPh	CH ₂ CH=CH	1,2-Phe	1,2-ethyne diyl	CONHSO ₂ -Ph
151	2-((4-FPh)CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	prop-2-yne-1,3-diyl	CONHSO ₂ -(5-Br-2-thienyl)

152	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH ₂ CH=CH	1,2-Phe	1,2- ethynediyl	CONHSO ₂ -Me
153	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	CONHSO ₂ -(2,5- (MeO) ₂ Ph)
154	6-((4-FPh)CH ₂ O)- 2-naphthyl	CH ₂ CH=CH	4-F-1,2-Phe	1,2-c-Pr	CONHSO ₂ -(3- MePh)
155	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	CONHSO ₂ -(4- MePh)
156	4-HO-3-(MeO)Ph	CH ₂ CH=CH	1,2-Phe	1,2-c-Pr	CONHSO ₂ -n-Bu
157	4-((4-FPh)CH ₂ O) -1-naphthyl	CH=CHCH ₂	1,2-Phe	1,2-c-Bu	CONHSO ₂ -(2- Cl-4-FPh)
158	Ph	CH ₂ CH=CH	1,2-Phe	CH=CH	CONHSO ₂ -(2- MePh)
159	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CONHSO ₂ - c-Pr
160	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	CO ₂ H
161	4-((2,4-F ₂ Ph) CH ₂ O)-3-(MeO)Ph	(CH ₂) ₃	4-F-1,2-Phe	CH=CH	1H-tetrazol- 5-yl
162	2-((4-FPh) CH ₂ O)Ph	CH=CHCH ₂	3-MeO- 1,2-Phe	CH=CH	1H-tetrazol- 5-yl
163	2,4-((4-FPh) CH ₂ O) ₂ Ph	CH=CHCH ₂	1,2-Phe	CH=CH	1H-tetrazol- 5-yl
164	4-HO-3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	1,2-c-Pr	1H-tetrazol- 5-yl
165	Ph	CH=CHCH ₂	1,2-Phe	(CH ₂) ₂	1H-tetrazol- 5-yl
166	2-((4-FPh)CH ₂ O) -3-(MeO)Ph	CH=CHCH ₂	1,2-Phe	CH=CH	SO ₃ H
167	2-((4-FPh)CH ₂ O) -3-MePh	(CH ₂) ₃	4-F-1,2-Phe	(CH ₂) ₂	SO ₃ H

5

wherein X⁺ represents a cation.

17. A compound in accordance with claim 16
 wherein X⁺ represents a cation selected from the group consisting
 of: ammonium, calcium, magnesium, potassium and sodium.

10

18. A pharmaceutical composition comprised of a
 compound in accordance with any one of claims 1 to 17 in
 combination with a pharmaceutically acceptable carrier.

15

19. A pharmaceutical composition in accordance
 with claim 18 further comprising a COX-2 selective inhibiting
 compound.

5

20. A method of treating or preventing a prostaglandin mediated disease in a mammalian patient in need thereof, comprising administering to said patient a compound in accordance with claim 1 in an amount which is effective for treating or preventing said prostaglandin mediated disease.

21. A method of treating or preventing a prostaglandin mediated disease in accordance with claim 20 further comprising administering to said patient an effective amount of a COX-2 selective inhibiting compound.

22. A method of treating or preventing a prostaglandin mediated disease in accordance with claim 20 wherein the prostaglandin mediated disease is selected from the group consisting of:

20 Pain, fever, inflammation, rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains, strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout,

25 ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases, cellular neoplastic transformations, metastatic tumor growth, prostaglandin-mediated proliferation disorders such as diabetic retinopathy and tumor angiogenesis, dysmenorrhea, premature

30 labor, asthma, eosinophil related disorders, Alzheimer's disease, glaucoma, bone loss (osteoporosis), promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

23. A method of treating or preventing an E type prostaglandin mediated disease in a mammalian patient, comprising administering to said patient an amount of an E type prostaglandin ligand in an amount which is effective to treat or prevent said E type prostaglandin mediated disease.

24. A method in accordance with claim 23 further comprising administering a COX-2 selective inhibitor.

5 25. An antagonist of pain and inflammatory effects of E-type prostaglandins pharmaceutical composition, comprising an acceptable antagonizing amount of a compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, in association with a pharmaceutically acceptable carrier.

10 26. A compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, for use in the prevention or treatment of prostaglandin mediated diseases in a mammalian patient.

15 27. Use of a compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, in the manufacture of a medicament for the treatment or prevention of prostaglandin mediated diseases in a mammalian patient.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00926

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C59/66 C07C309/10 C07C311/51 C07C323/60 C07C323/62
 C07D215/14 C07D215/36 C07D257/04 C07D285/12 C07D307/79
 C07D317/60 C07D333/34 A61K31/192 A61K31/381

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 780 061 A (A. ALLAIS, ET AL.) 18 December 1973 (1973-12-18) column 26, line 40 - line 57	1,3-5,7
X	CH 407 101 A (J.R. GEIGY) 31 August 1966 (1966-08-31) page 2, line 35	1,3-5,7
X	US 3 641 133 A (E.E. GALANTAY, ET AL.) 8 February 1972 (1972-02-08) example 15	1,3-5,7
X	US 4 922 022 A (J. DIXON, ET AL.) 1 May 1990 (1990-05-01) column 9, line 34 - line 35	1,3-5,7
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 December 1999

Date of mailing of the international search report

11/01/2000

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English, R

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/CA 99/00926

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.M. SPRINGER, ET AL.: "The reaction of 1-tetralones with potassium hydroxide-sodium hydroxide" JOURNAL OF ORGANIC CHEMISTRY, vol. 35, no. 5, May 1970 (1970-05), pages 1260-1264, XP002126076 American Chemical Society, Washington, DC, US ISSN: 0022-3263 compounds 17-20	1
X	R.F. REKKER, ET AL.: "Ultraviolet absorption spectra of some aromatic tricyclic ketones" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol. 90, 1971, pages 343-351, XP000857564 Elsevier Science Publishers, Amsterdam, NL ISSN: 0165-0513 page 350, line 16 - line 21	1,3-5,7
A	W0 96 06822 A (ZENECA) 7 March 1996 (1996-03-07) cited in the application page 1 -page 3	1,18,20, 23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/ 00926

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: **not applicable**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 99 00926

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: not applicable

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds having values of the variables Ar1, W, Ar2, X and Q illustrated in examples 1-3, 6-48, 50, 51, 58, 59, 61, 70-75, 77-84 (ie. those compounds of claim 16 with at least one physical property reported in the description).

Even after this limitation, the search revealed such a large number of particularly relevant documents, in particular with regard to novelty, that the drafting of a comprehensive International Search Report is not feasible. The cited documents are considered as to form a representative sample of the revealed documents, duly taking into account their relevance with respect to the subject-matter as illustrated by the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00926

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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